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CONTENTS OF VOLUME 49

JANUARY 1943. NUMBER 1

	PAGE
Regenerative Capacity of Ventral Roots After Avulsion from the Spinal Cord. Sarah S. Tower, Ph.D., M.D., Baltimore.....	1
Studies in Diseases of Muscle. XI. Progressive Muscular Atrophy: Report of a Case with Unusual Features; Effect of Prostigmine and Physostigmine on Fasciculations; Metabolism of Ascorbic Acid. A. T. Milhorat, M.D., and T. P. Almy, M.D., New York.....	13
Fascicular Muscle Twitchings in Amyotrophic Lateral Sclerosis: Their Origin. Roy Laver Swank, M.D., Ph.D., and Jerry C. Price, M.D., New York....	22
Familial Type of Paralysis in Infants and Its Relationship to Other Heredo- familial Disorders: A Clinicopathologic Study. Albert J. Lubin, M.D., San Francisco; Otto Marburg, M.D., New York, and K. Tamaki, M.D., San Francisco.....	27
Experimental Neuroses and Psychotherapy. Jules H. Masserman, M.D., Chicago	43
Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: V. Capillaries of the Finger Nail Fold. Harry A. Paskind, M.D., and Meyer Brown, M.D., Chicago.....	49
Intracranial Dermoid and Epidermoid Tumors. Major John Martin and Lieu- tenant Colonel Loyal Davis, Medical Corps, Army of the United States...	56
Sibling Deaths in the Anamneses of Schizophrenic Patients. Saul Rosenzweig, Ph.D., and Douglas Bray, M.A., Worcester, Mass.....	71
Distribution of Iodine in Blood Serum and in Cerebrospinal Fluid. Edwin F. Gildea, M.D., and Evelyn B. Man, Ph.D., New Haven, Conn.....	93
Functional Representation in the Oculomotor and Trochlear Nuclei. Morris B. Bender, M.D., and Edwin A. Weinstein, M.D., New York.....	98
Fatalities Following Electric Convulsive Therapy: Report of Two Cases, with Autopsy. Franklin G. Ebaugh, M.D.; Clarke H. Barnacle, M.D., and Karl T. Neuburger, M.D., Denver.....	107
Acute Syphilitic Anterior Poliomyelopathic Syndrome: Report of a Case. Levellys F. Barker, M.D., Baltimore.....	118
Arterial Hypertension Following Metrazol Shock Therapy. William C. Men- ninger, M.D., Topeka, Kan.....	120
Technical and Occasional Notes: An Apparatus to Be Used in Recording Tremors. Arthur Allen Morris Jr., B.A., Durham, N. C.....	123
Abstracts from Current Literature.....	126
Society Transactions: Philadelphia Psychiatric Society and Philadelphia Psychoanalytic Society.	140
Chicago Neurological Society.....	145
Book Reviews.....	150

FEBRUARY 1943. NUMBER 2

Amyotrophic Lateral Sclerosis and Related Conditions: A Clinical Analysis. Captain Roy Laver Swank, Medical Corps, Army of the United States, and Tracy J. Putnam, M.D., New York.....	151
Histogenesis of the Early Lesions of Multiple Sclerosis: I. Significance of Vascular Changes. I. Mark Scheinker, M.D., Cincinnati.....	178
Effect on the Electroencephalogram of Changing the Blood Sugar Level. Pauline A. Davis, M.A., Cambridge, Mass.....	186
Results of Insulin and Epinephrine Tolerance Tests in Schizophrenic Patients and in Normal Subjects. H. Freeman, M.D.; J. M. Looney, M.D.; R. G. Hoskins, M.D., and Cora G. Dyer, M.A., Worcester, Mass.....	195
Cerebral Dysrhythmia in Relation to Eclampsia. Milton Rosenbaum, M.D., and George L. Maltby, M.D., Cincinnati.....	204

FEBRUARY—*Continued*

	PAGE
Intracranial Epidermoids Occurring Simultaneously Below and Above the Tentorium. Howard A. Black, M.D., Brooklyn.....	214
Pseudojacksonian Epilepsy in Children. Major John E. Scarff, Medical Corps, Army of the United States.....	223
Midbrain Deafness: Tumor of the Midbrain Producing Sudden and Complete Deafness. Paul Sloane, M.D.; A. Persky, M.D., and M. Saltzman, M.D., Philadelphia	237
Atypical Seizures Elicited by Electrical Stimulation of the Cerebrum in the Cat. J. Thomas Payne, M.D.; Sam L. Clark, M.D., Ph.D.; James W. Ward, M.D., Ph.D., and Frederic E. Cowden, M.D., Nashville, Tenn.....	244
Paraphenylenediamine Poisoning with Changes in the Central Nervous System. Charles Davison, M.D., New York.....	254
Treatment of Schizophrenia: Follow-Up Results in Cases of Insulin Shock Therapy and in Control Cases. Jacques S. Gottlieb, M.D., and Paul E. Huston, M.D., Ph.D., Iowa City.....	266
Statistical Control Studies in Neurology: I. The Babinski Sign. Nathan Savitsky, M.D., and M. J. Madonick, M.D., New York.....	272
Case Reports:	
Aberrant Thyroid Tumor of the Vertebrae with Compression of the Spinal Cord: Recovery After Operation and High Voltage Roentgen Therapy. Peter G. Denker, M.D., and Raymond L. Osborne, M.D., New York.....	277
News and Comment.....	282
Abstracts from Current Literature.....	283
Society Transactions:	
New York Neurological Society and New York Academy of Medicine, Section of Neurology and Psychiatry.....	296
Philadelphia Psychiatric Society.....	302
Boston Society of Psychiatry and Neurology.....	308
Book Reviews.....	320

MARCH 1943. NUMBER 3

Experimental Studies on Headache: Analysis of the Headache Associated with Changes in Intracranial Pressure. E. Charles Kunkle, M.D.; Bronson S. Ray, M.D., and Harold G. Wolff, M.D., New York.....	323
Predisposing Factors in Bromide Intoxication. Andras Angyal, M.D., Worcester, Mass.....	359
Meningeal Gliomatosis Secondary to Intramedullary Glioma. Roma Amyot, M.D., Montreal, Canada.....	383
Sequels of Equine Encephalomyelitis. H. H. Noran, M.D., and A. B. Baker, M.D., Minneapolis.....	398
Attempts at Treatment of Schizophrenia and Other Nonepileptic Psychoses with Dilantin. Lothar B. Kalinowsky, M.D., and Tracy J. Putnam, M.D., New York.....	414
Effect of Extremes of Environmental Change on Man. Lewis J. Pollock, M.D., Chicago.....	421
Effect of Autonomic Drugs on Cerebrospinal Fluid Pressure in Schizophrenic and Other Psychoses: I. Effect of Histamine. Emerick Friedman, M.D., and Thomas Thale, M.D., Norwich, Conn.....	449
Clinical, Technical and Occasional Notes:	
Electrical Skin Resistance Technic Used to Map Areas of Skin Affected by Sympathectomy and by Other Surgical or Functional Factors. Fred G. Whelan, B.E., and Curt P. Richter, Ph.D., Baltimore.....	454
Obituaries:	
Stephen Walter Ranson, M.D.....	457
Abstracts from Current Literature.....	464
Society Transactions:	
Chicago Neurological Society.....	475
Michigan Society of Neurology and Psychiatry.....	478
Philadelphia Neurological Society.....	479
Book Reviews.....	487

APRIL 1943. NUMBER 4

	PAGE
Grouping Behavior of Normal Persons and of Persons with Lesions of the Brain: Further Analysis. Ward C. Halstead, Ph.D., and Paul H. Settlage, Ph.D., Chicago	489
Calcification of the Cerebral Cortex Associated with a Meningotheliomatous Meningioma: Pathologic Study, with Comment on Incomplete Types of the Neurocutaneous Syndrome. Ben W. Lichtenstein, M.D., and Maurice Lev, M.D., Chicago.....	507
Neurogenic Hyperthermia and Its Treatment with Soluble Pentobarbital in the Monkey. Captain L. E. Beaton, Medical Corps, Army of the United States, and C. Leininger, M.S.; W. A. McKinley, B.A.; H. W. Magoun, Ph.D., and S. W. Ranson, M.D., Chicago.....	518
Myasthenia Gravis: Curare Sensitivity; A New Diagnostic Test and Approach to Causation. A. E. Bennett, M.D., Omaha, and Captain Paul T. Cash, Medical Corps, Army of the United States.....	537
Disturbances in Parotid Secretion in an Unusual Neurologic Syndrome. Louis Linn, M.D., and Leo A. Spiegel, M.D., New York.....	548
Treatment of Post-Lumbar-Puncture Headache with Ergotamine Tartrate. Samuel A. Guttman, Ph.D., M.D., New York.....	556
Juvenile Amaurotic Idiocy: A Clinicopathologic Study. Albert J. Lubin, M.D., San Francisco, and Otto Marburg, M.D., New York.....	559
Surgical History of Trigeminal Neuralgia. Arnold M. Meierowsky, M.D., and Feori F. Pipito, M.D., Albany, N. Y.....	574
Foreign Body Granulomas Produced by Surgical Cotton. Frank H. Mayfield, M.D., and William McKee German, M.D., Cincinnati.....	581
Comparison of Metrazol Convulsive Therapy with Electric Shock in Treatment of Schizophrenia: Evaluation of Results Obtained in Treatment of One Hundred Schizophrenic Patients with Electric Shock. Leon Reznikoff, M.D., Secaucus, N. J.....	587
Neuropsychiatric Sequelae of Partial Exsanguination. J. P. Murphy, M.D., Washington, D. C.....	594
News and Comment.....	599
Abstracts from Current Literature.....	600
Society Transactions:	
American Association of Neuropathologists.....	615
Philadelphia Psychiatric Society.....	629
Chicago Neurological Society.....	633
Book Reviews.....	637

MAY 1943. NUMBER 5

Studies in Diseases of Muscle. A. T. Milhorat, M.D., and H. G. Wolff, M.D., New York:	
XII. Heredity of Progressive Muscular Dystrophy; Relationship Between Age at Onset of Symptoms and Clinical Course.....	641
XIII. Progressive Muscular Dystrophy of Atrophic Distal Type. Report on a Family; Report of Autopsy.....	655
Experiences with Intramedullary Tractotomy: II. Immediate and Late Neurologic Complications. Laurence M. Weinberger, M.D., Chicago, and Francis C. Grant, M.D., Philadelphia.....	665
Spinal Necrosis and Softening of Obscure Origin: Necrotic Myelitis Versus Myelomalacia; Review of Literature and Clinicopathologic Case Studies. Lieutenant Daniel Jaffe, Medical Corps, Army of the United States, and Walter Freeman, M.D., Ph.D., Washington, D. C.....	683
Inclusion Bodies and Late Fate of Ganglion Cells in Infantile Amaurotic Family Idiocy. Otto Marburg, M.D., New York.....	708
Fatal Cerebrovascular Accident Associated with Catatonic Schizophrenia: Report of a Case. J. P. Murphy, M.D., and Meta A. Neumann, M.S., Washington, D. C.....	724
Dr. H. Douglas Singer's Concept of the Psychoses. Irene C. Sherman, M.D., Ph.D., and Samuel B. Broder, M.D., Chicago.....	732

MAY—Continued

	PAGE
Pathways for Pain from the Stomach of the Dog. Oscar J. Balchum, M.Sc., and H. M. Weaver, Ph.D., Detroit.....	739
Formation of Demyelinated Plaques Associated with Cerebral Fat Embolism in Man. I. Mark Scheinker, M.D., Cincinnati.....	754
Occlusion of the Anterior Inferior Cerebellar Artery. Raymond D. Adams, M.D., Boston.....	765
News and Comment.....	771
Society Transactions:	
New York Neurological Society and New York Academy of Medicine, Section of Neurology and Psychiatry.....	773
Philadelphia Neurological Society.....	780
Philadelphia Psychiatric Society.....	786
Book Reviews.....	792

JUNE 1943. NUMBER 6

Electroencephalographic Foci Associated with Epilepsy. Erna L. Gibbs; H. Houston Merritt, M.D., and Frederic A. Gibbs, M.D., Boston.....	793
Effect of Electrical Stimulation on Atrophy of Denervated Skeletal Muscle. D. Y. Solandt, M.D.; D. B. DeLury, Ph.D., and John Hunter, M.A., Toronto, Canada.....	802
Interaction of Electric Shock and Insulin Hypoglycemia: Experimental Investigations. E. Gellhorn, M.D., Ph.D., and M. Kessler, M.S., Chicago.....	808
Studies on the Corpus Callosum: IX. Relationship of the Grasp Reflex to Section of the Corpus Callosum. Andrew J. Akelaitis, M.D.; Wilford A. Risteen, M.D., and William P. Van Wagenen, M.D., Rochester, N. Y....	820
Experimental Swelling of the Brain. S. Obrador and J. Pi-Suñer, Mexico, Mexico.....	826
Schizophrenic Language. John C. Whitehorn, M.D., Baltimore, and George Kingsley Zipf, Ph.D., Cambridge, Mass.....	831
Oral and Intravenous Dextrose Tolerance Curves of Patients with Manic-Depressive Psychosis. E. F. Gildea, M.D.; V. L. McLean, B.A., and E. B. Man, Ph.D., New Haven, Conn.....	852
Syndrome of Involvement of the Posterior Cord of the Brachial Plexus. Russell N. DeJong, M.D., Ann Arbor, Mich.....	860
Encephalopathy Following Intravenous Administration of Arsenical Preparations. David A. Boyd Jr., M.D., and Louis Nie, M.D., Indianapolis.....	863
Retrograde Degeneration: Effect of Hemisections on the Homolateral Axons of the Spinal Cord. A. M. Lassek, M.D., Ph.D., Charleston, S. C.....	878
Cervical Syringomyelia and Syringomyelia-Like States Associated with Arnold-Chiari Deformity and Platybasia. Ben W. Lichtenstein, M.D., Chicago...	881
Case Reports:	
Permanent Damage to the Nervous System Following an Attack of Polyradiculoneuritis (Guillain-Barré Syndrome): Report of a Case, with Necropsy. William O. Russell, M.D., and Walter L. Moore, M.D., St. Louis.....	895
Clinical, Technical and Occasional Notes:	
Myasthenia Gravis: Familial Occurrence. Henry Alsop Riley, M.D., and Maurice Frocht, M.D., New York.....	904
News and Comment.....	909
Abstracts from Current Literature.....	910
Society Transactions:	
Boston Society of Psychiatry and Neurology.....	919
Chicago Neurological Society.....	924
Michigan Society of Neurology and Psychiatry.....	926
Book Reviews.....	930
General Index.....	931

REGENERATIVE CAPACITY OF VENTRAL ROOTS AFTER AVULSION FROM THE SPINAL CORD

SARAH S. TOWER, PH.D., M.D.

BALTIMORE

The object of this paper is to prove unfounded the prevailing assumption that ventral nerve roots cannot regenerate if avulsed from the spinal cord. That they do not regenerate in man is general clinical experience, certainly. Yet in exploring to their limits the regenerative capacities of various parts of the nervous system, one may find that clinical experience is a too conservative guide. One would like to know whether the failure to regenerate is primarily one of the nerve tissue or is secondarily due to obstacles interposed. If the latter, surgical intervention may be at least considered. If the former, the condition is perhaps still not irremediable, but the approach will be through other than surgical channels. The present report is concerned with demonstrating that in cats avulsion of ventral spinal roots is compatible with regenerative activity on the part of the neurons involved, even to the extent of functional reinnervation of denervated muscle. With full realization that species and age influence greatly the vigor of regenerative processes in the peripheral nervous system, and that the cat ranks high in respect to that function and man low, the observations are nevertheless offered as an invitation to reexamine the regenerative capacity of nervous tissue similarly damaged in man.

EVIDENCE

Procedure.—Four young adult cats were used. In 3 of these animals the right ventral roots from the sixth cervical to the second thoracic segment were separated from the dorsal roots extradurally and cut distally, at their junction with the dorsal root ganglia. The dural investment of each ventral root was then clipped and slit around the stump until the fan of rootlets was exposed. These were clamped lengthwise in a fine, curved clamp and pulled from the cord, centrally, with a steady even pull to bring out as long a stump as possible. By this procedure the dural investment of the cord was left intact except that immediately surrounding each emerging ventral root. In the fourth animal only three roots, the seventh cervical to the first thoracic, were so treated, but, in addition, the dorsal roots and ganglia were excised, not avulsed, which emptied the intervertebral

From the Department of Anatomy, Johns Hopkins University.

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foramens of nerve tissue. This last animal was killed after four weeks, and the other 3 after four, six and twelve months, respectively. All the animals were fixed by intra-aortic injection of a 20 per cent concentration of neutral solution of formaldehyde U. S. P., after preliminary flushing of the vascular system with saline solution. Observations were made on the living animals, on the spinal cords at autopsy and on microscopic preparations of affected parts of the cords and skeletal musculature.

Observations on the Living Animals.—During life the cats exhibited an extent of motor paralysis consistent with their lesions: with five roots cut, complete paralysis of the musculature of the related extremity, and with three roots cut, somewhat less. The paralyzed muscles wasted and contracture resulted. There was also a partial Horner syndrome in the eye on the side of the operation. The animals surviving six months or less made no appreciable recovery of the lost motor functions, even the partial Horner syndrome persisting. During the second half-year, however, the animal surviving longest gradually reestablished some unquestionable control of the skeletal musculature, useful at the shoulder and elbow and demonstrable as fascicular twitches, and even coarser contractions, in the flexors and extensors of the forearm in response to passive stretch. The toes were still tightly fixed in contracture. The partial Horner syndrome was still in evidence, although minimal. Functionally, the large motor fibers had made appreciable recovery, and possibly the smaller preganglionic sympathetic fibers as well.

Autopsy Observations.—The five segments of the cord selected for histologic preparation were not closely examined; that is, the meninges and scar were not disturbed. The remaining segments, thirteen in all, were carefully freed of loose tissue, including the dura, to expose the area for emergence of ventral rootlets. The dorsal rootlets were clipped to improve the view from that direction. In every segment so examined ventral rootlets were clearly to be seen, emerging from the cord. The longer the duration since operation, the better were they developed, but at four months, the earliest of these gross examinations, they were clearly defined and were whitish, as though myelinated. The most cephalad rootlets of a segment were often distinctly thicker and more myelinated in appearance than the middle and caudal segments, an observation suggesting that these longer and obliquely coursing rootlets had been less severely damaged at avulsion. Even at operation it had been evident that some rootlets were breaking off short or just flush with the surface of the cord while others were pulling out fairly deeply. All the grossly visible rootlets turned laterally and plunged into the dense scar tissue, closing the apertures in the dura, where they could be followed no farther. In 1 animal, which survived four months, just dorsal to each of the five reconstituting ventral roots the cord had herniated laterally to form a round nodule 1 to 2 mm. in diameter,

with lateral distortion of both the white and the gray matter, closely confined to that portion only, of each segment. Curiously, in no other animal did anything corresponding to this develop; yet there is nothing in the operative records to explain this singular occurrence.

Microscopic Study of Spinal Roots and Cord.—Specimens consisting of an entire segment of the cord together with the attached roots and ganglion of each side and scar on the one side were prepared according to Cuajunco's¹ modification of Bielschowsky's silver technic and sectioned in series transversely at 15 microns. Figure 1 shows one of these sections. From the cat killed after four weeks all three segments, from the seventh cervical to the first thoracic, were taken, but from the cats surviving four and six months the eighth cervical segment only was used. No histologic preparations were made from the cord of the animal surviving a year, the prior examination of the

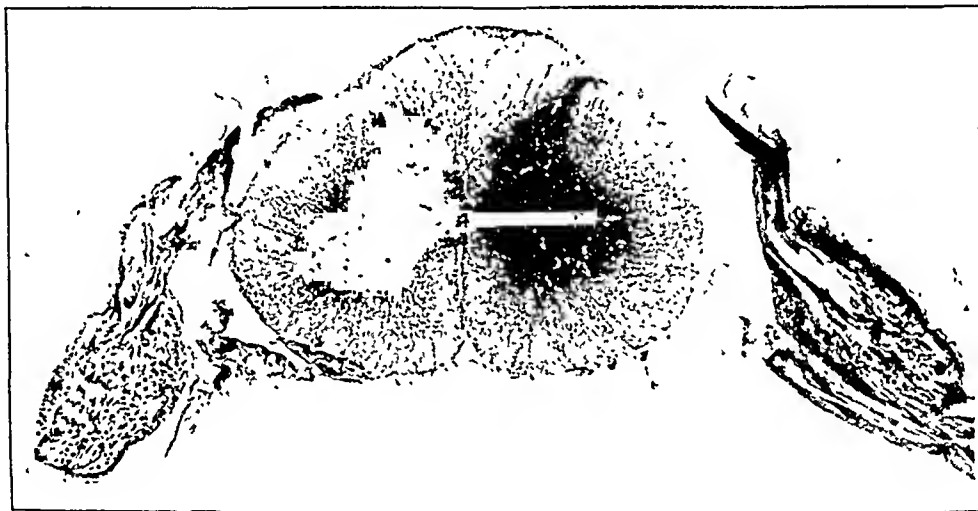


Fig. 1.—Section of spinal cord and roots from the caudal end of the eighth cervical segment four months after avulsion of the right ventral roots (the left side in the photograph). Note the shrunken anterior horn and the reduced thickness of the anterolateral white column, the tracts of emergent rootlets on both sides and the mat of regenerating fibers formed over the emerging rootlets on the affected side. Bielschowsky silver stain.

other specimens and the gross examination having made fairly certain what one could expect to find.

Microscopic examination of the sections of the cord showed even at first glance the tremendous vigor of the regenerative process in every animal. Emerging from the spaces normally emitting the ventral rootlets were nerve fibers, few and fine in the cat surviving one month; more numerous, and both fine and unmyelinated and larger and myelinated, with longer survival. Figure 2 *B*, *D* and *E* show such rootlets

1. Cuajunco, F.: Embryology of the Neuromuscular Spindle, *Contrib. Embryol.* 19:45, 1927.

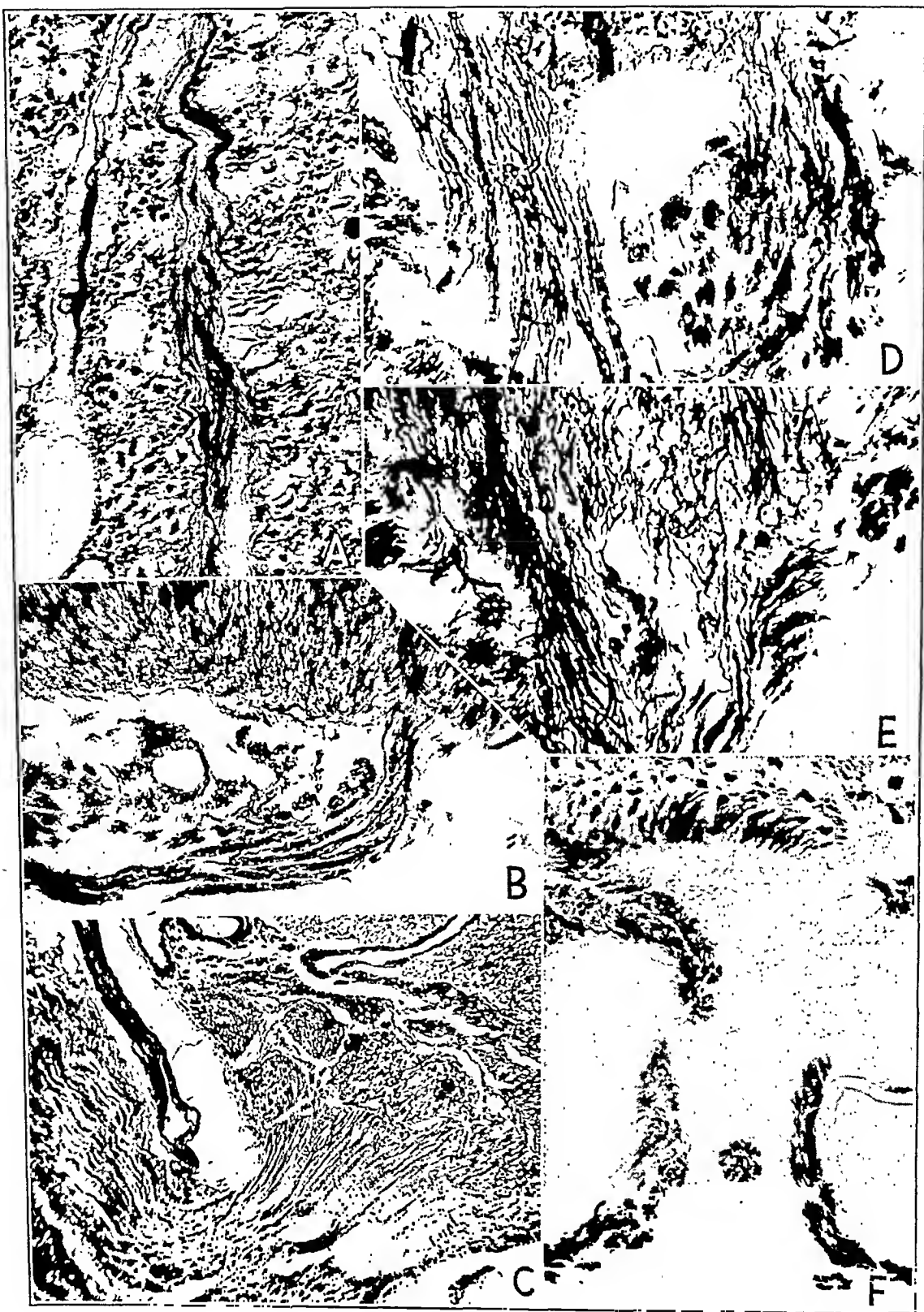


Figure 2

(See legend on opposite page)

after six months' survival. By far the greater number of these fibers turned decidedly laterally, as seen in *B*, and reconstituted the rootlets which were grossly visible at autopsy. Figure 2 *C* shows one of the larger collections of regenerating fibers forming out of a mat of fibers at the surface of the cord and sweeping laterally toward the intervertebral foramen.

More striking, however, than these regenerating rootlets were the single fibers and small groups which escaped from the main bundles into the arachnoid tissue. There they multiplied in a riotous fashion into a prodigious number of unmyelinated and intensely argyrophilic fibers, which filled the loose connective tissue of the meninges, formed dense layers in the adventitia around blood vessels and ran in clusters and larger bundles in all directions. Figure 2 *B*, *D* and *E* show such fibers leaving the emerging rootlets, and figure 2 *F*, the dense investment of a good-sized artery and vein and smaller bundles in the arachnoid. The directions of growth of these vagrant fibers were interesting. The meninges dorsolateral and ventromedial to the line of emerging root fibers seemed equally open to them, with the adventitia of blood vessels especially inviting. At one month they had penetrated the ventromedian sulcus to its depth. Fiber bundles were present dorsal to the dorsal roots, however, only in the cat in which the dorsal roots were also removed. The region of intact ventral roots on the other side of the cord was, as it were, hostile territory; the regenerating fibers approached, but did not enter regardless of how long the elapsed time since operation: four weeks or six months. Some small fiber bundles penetrated the cord again in the adventitia of blood vessels, and where this took place far laterally, their being emergent fibers was

EXPLANATION OF FIGURE 2

Unretouched photomicrographs of Bielschowsky silver preparations.

A, tract of regenerating ventral rootlet deep in the white matter of the seventh cervical segment four weeks after avulsion of the ventral roots. Magnification $\times 333$. *B*, emerging ventral rootlet six months after avulsion. The fibers inside the cord are unmyelinated and intensely argyrophilic, but just outside they begin to myelinate. Magnification $\times 55$. *C*, large-sized rootlet forming from a dense mat of regenerating fibers at the surface of the cord and sweeping laterally toward the intervertebral foramen, six months after avulsion of the ventral roots. Magnification $\times 25$. *D*, two small ventral rootlets emerging from an uninjured part of the cord surface and remyelinating as they turn laterally. Magnification $\times 120$. *E*, two similar small rootlets emerging from a region of injury to the surface of the cord, with fibers sweeping out from the white matter of the anterior column between them. Magnification $\times 120$. *F*, regenerating nerve fibers filling the adventitia of a medium-sized vein (left) and artery (right) and forming bundles in the arachnoid four weeks after avulsion of the ventral roots. Magnification $\times 333$.

out of the question. But this was a rare occurrence. No fibers grew in or on the dura where it was free of scar tissue. The scar filling the intervertebral foramen showed the usual florid picture of fibers growing in a moderately dense connective tissue, with many examples of spiral formation and fountain spraying. And the reconstituted rootlets, many of which were fairly well ordered as long as they lay in loose arachnoid tissue, plunged into this scar and were confounded. Here and there, as shown in figures 1 and 2 *C*, regenerating fibers had formed dense, tangled mats applied to the surface of the cord in the region of the emerging rootlets, especially where the pial membrane was damaged. These tended to disorder the reformation of the rootlets, although the large rootlet shown in figure 2 *C* arose in just such a plaque.

Within the spinal cord, the tracts for emergence of ventral root fibers were clear in all the specimens—obviously, the preexisting tracts. Figure 1 shows them at a low magnification, and figure 2 *A*, at a higher. Some had few or perhaps no fiber occupants; most had a number. There was plain evidence of sclerosis in some of the tracts, the fibrous tissue being laid down lengthwise, and little evidence of it in others. Adjacent tracts might be sclerosed, the one heavily and the other little, if at all, and nerve fibers seemed to emerge equally freely regardless of these conditions.

The fibers emerging along the tracts varied greatly in appearance, which depended partly on the time of survival and partly, apparently, on the accident of how deeply individual fibers were torn out. The four week specimens contained more fibers that compared favorably with the control side for size and myelination than did the longer-surviving specimens. These appeared to be fibers which had broken off short and still retained their original myelination. In the specimens taken later, perhaps because the avulsion was more thorough, or perhaps because the sclerosis resulted in subsequent demyelination, there were few such fibers. In all the specimens, however, by far the greater number of fibers in the tracts, even deep in and adjacent to the gray matter, were fine, intensely argyrophilic, seemingly unmyelinated and often irregular in their course—typical regenerating fibers. Figure 2 *A* shows some of these from deep within the white matter at four weeks.

Throughout all these variously disposed masses and bundles of regenerating fibers, both inside and outside the cord, multiplication was going on. The divisions, usually by multiple longitudinal splitting, could be seen deep within the rootlet tracts in the cord, as in figure 2 *A*, and more often just inside the cord. But the numbers of fibers leaving the cord were still relatively few, and the rootlet bundles were loosely formed, as shown in figures 2 *B* and *D*. Immediately outside the cord, how-

ever, division accelerated rapidly, producing, as the bundles passed distally, the densely packed reconstituted rootlets and giving rise to the sprouts to the arachnoid tissue. Figure 2 *B* and *D* show the quantity of this multiplication in rootlets as little involved in injury or scarring of the cord as could be found; figure 2 *C* and *E*, the quantity apparently stimulated by graver injury to the cord.

If one may judge the amount of opposition to the regenerating fibers as in proportion to their multiplication, especially to the fantastic forms which this takes, the tracts within the cord must be fairly open and easily traversed. Resistance is met first at the passage from the tracts into the pia-arachnoid, and increasingly from that point distally, out to the dural scar. Certainly, end knobs, such as generally indicate blockage of growth in either the central or the peripheral nervous system, were not seen at all in the tracts; the multiplication of fibers there was not excessive, and spirals and other complicated figures of impeded regeneration were seen at the exit only, and rarely even there. In contrast, all these were increasingly in evidence from the point of emergence of the rootlets laterally to the intervertebral foramen. In a previous publication by Westbrook and me² dealing with the dorsal roots of the four week specimens, we could not resist publishing the best picture obtained of one of these spirals at the point of emergence.

In the specimens taken at one month the regenerating fibers did not appear to be remyelinated, though without a specific myelin stain this does not mean that no remyelination had taken place. In the specimens taken at four and six months, although myelinated fibers were almost wanting deep within the rootlet tract in the cord, numbers of fibers just inside and leaving the cord were heavily myelinated, presenting a fairly normal appearance. Especially was this true of fibers turning laterally from the point of emergence in the reconstituted rootlets. Characteristically, the fibers began to be myelinated a little distance from their emergence from the cord, as is apparent in figure 2 *B* and *D*, the bulk of the fibers showing at their emergence, as in their course within the cord, the intense silver staining of unmyelinated regenerating axons. Even in the best reconstituted rootlets, however, the myelinated fibers were still greatly outnumbered by the unmyelinated fibers clustering between them. And spirals and other fantastic formations of unmyelinated axons frequently invested the myelinated fibers. Only rarely were the fibers exploring the meninges or filling the adventitia of blood vessels myelinated.

2. Westbrook, W. H. L., Jr., and Tower, S. S.: An Analysis of the Problem of Emergent Fibers in Posterior Spinal Roots, Dealing with the Rate of Growth of Extraneous Fibers into the Roots After Ganglionectomy, *J. Comp. Neurol.* **72**: 383, 1940.

Although regenerating ventral rootlets were the most conspicuous source of fibers for the florid growth seen in the specimens they were not the only one. The white matter of the anterior column also contributed, and in no small way, though only where the surface of the cord had been injured. The surface layer of arachnoid-pia-neuroglia appeared to be impenetrable to nerve fibers from either side so long as it was intact. The regenerating fibers clambered in hordes over its outer surface but entered the cord only in the adventitia of blood vessels, while from inside fibers emerged only in what were clearly pre-existing rootlet tracts. But where this characteristically staining surface layer was injured, as had happened in a number of places, the fibers of the white matter poured out to join the proliferating swarm. Figure 2E shows this in its most frequent occurrence, between two closely adjacent rootlets, themselves also regenerating, where the surface layer had apparently been torn away in the avulsion. What might be the end result of this growth, should fibers of such origin ultimately terminate in motor end plates on skeletal muscle, cannot be hazarded.

Deeper than the surface, the white matter of the cord was gravely damaged only in the specimens taken at four weeks. These showed much fiber loss of traumatic origin in both the ventral and the lateral column, as well as the emptying of the posterior column due to section of the dorsal roots. Avulsion of the other ventral roots was apparently more smoothly executed, and with the longer passage of time the debris was cleared up and the spaces closed in. But comparison in figure 1 of the thickness of the white matter in the region of emerging ventral rootlets on the two sides gives a measure of the fibers lost.

The anterior horn on the side of operation was noticeably smaller in area than that on the control side in every specimen. Figure 1 shows the difference at four months. On looking more closely, one saw that a great number of cells had disappeared altogether from all specimens, though in the specimens taken at four weeks some debris could usually be made out. But more significant than this destruction is the fact that many of the cells had survived the trauma of having their axons torn out. A rough estimate of the percentage of cells surviving was attempted, as an index to the number of ventral root fibers potentially available for regrowth. The four week specimens had suffered far the gravest loss of cells, the seventh cervical segment on the side of operation possessing never more than half the cell complement of the control side. In ten sections selected at random 1 to 19 large motor type cells were counted on the affected side, as compared with 36 to 46 cells for the control side. Possibly the additional trauma of the dorsal root section; with the attendant reduction in blood supply to the cord, may have contributed to this loss. In the longer-

surviving specimens the cell loss was exceedingly variable throughout the segments, and in the different cell groups in one section, the amount depending probably on the hazard of how deeply the rootlets were torn out. But nowhere did cell counts on the two sides show a loss greater than 50 per cent. Generally speaking, the more cephalic portions of the segments, where the roots were apparently less deeply avulsed, had suffered less. And the larger, more laterally situated cells were generally present in greater number than the smaller, more medially situated cells, possibly because the longer, curved track of the root fibers from the lateral cells cushioned, as it were, the shock of avulsion to a degree that the shorter, more direct course of the fibers from the ventromedial cells could not.

Although no Nissl stains were made, the cells surviving at four weeks looked sick, with eccentric nuclei and seemingly shrunken dendrites. By four months, however, and six months also, the surviving cells were healthy in appearance, and not noticeably smaller than corresponding cells on the control side, with their nuclei centrally located, neurofibrillae clearly stained and no visible pathologic features.

Microscopic Examination of Skeletal Muscle.—The entire fifth interosseous muscle from both forepaws and part of the fourth interosseous muscle were prepared according to the Bielschowsky silver method, the entire first muscle being cut longitudinally at 15 microns, the second, transversely at 10 microns.

Thorough examination of the specimens taken four months after root avulsion showed no motor end plates or motor nerve fibers, only sensory innervation. After six months, however, scattered patches of reinnervated muscle fibers could be found, although this reinnervation had not been detected functionally. Figure 3 shows one of the regenerating nerve fibers branching to form plaques on two muscle fibers. The reinnervated muscle fibers are thicker and more deeply staining than the noninnervated and atrophic fibers in the same field. And the accumulation of nuclei to form the sole plate is conspicuous even where the reinnervating fiber is of very immature appearance, in striking contrast to the lack of identifiable sole plates on atrophic fibers six months after denervation. Apparently, the reassembly of the appropriate nuclei takes place rapidly under the stimulus of reinnervation.

Within the nerve trunks the fibers were still sparse, and with the four month preparation as a standard, it seemed that most of them must be sensory or sympathetic. But among the muscle fibers, copious and somewhat erratic branching greatly increased their number. Up to the final branchings the regenerating fibers occupied neurilemma sheaths which appeared to have the disposition of the old nerve branches. Some of the more florid terminal branching seemed to be

free of this pattern. As they approached the muscle fibers, the reinnervating nerve fibers were unmyelinated and unusually argyrophilic. Within the nerve trunks the presence of the sensory and sympathetic fibers of all sizes made it impossible to distinguish the regenerating fibers with certainty, but groups of intensely argyrophilic fibers were suspect.

The specimens taken a year after root avulsion showed somewhat more extensive reinnervation than that just described, but still very immature. None of these interosseous muscles had recovered function



Fig. 3.—Regenerating nerve fiber branching and forming motor end plates on two muscle fibers. Magnification $\times 615$.

sufficient to enable the cat to spread the toes when reaching for support. And the toes were still firmly flexed and adducted in contracture.

CONCLUSION

The assumption that ventral nerve roots cannot regenerate if avulsed from the spinal cord is clearly unfounded as a general proposition. Avulsion of the ventral roots in cats, causing some fibers to break off outside the cord, others flush with the cord and still others deep within the cord, damages many of the related anterior horn cells

irremediably so that they degenerate and disappear. But many cells also survive and regenerate their axons. The regenerating axons can be seen growing and multiplying in the rootlet tracts deep within the cord with singularly little evidence of obstruction until they emerge into the mesodermal connective tissues. And even there some factor operates to converge the reforming rootlets toward the intervertebral foramens; perhaps an attraction emanating from the scar tissue in the dural apertures or from the distal cut end of the ventral root, or, more likely, a directional organization of the scar tissue in the arachnoid along the lines of the avulsion.

While still within the cord, the regenerating ventral root fibers are strikingly not subject to the conditions which block regrowth of nerve fibers generally within the central nervous system. Moreover, the ventral root exit does not present the impenetrable barrier to growing nerve fibers that the dorsal root entry does (Tower³). More detailed knowledge of the arrangement of the supporting tissues in these two junctional zones might throw light on such significant differences, especially, perhaps, in relation to the development of the neuroglia-neurilemma sheaths of the two roots. Recent experimental study of the sheathing of root fibers in chick embryos (Jones⁴) has indicated that the neural crest gives rise to the sheath cells of the dorsal root, and the neural tube, to the sheath cells of the ventral root which migrate out along the fibers. With neuroglia and neurilemma developing thus in continuity from within the cord to the periphery on the ventral root fibers, it is understandable that the rootlet tract should offer no special obstacle to regeneration of these fibers. In the dorsal root, on the contrary, where the two tissues meet secondarily, making a sharply defined junction, this junction, also understandably, clearly offers the first impediment to the reentry of growing nerve fibers (Tower³).

That the cat can repair avulsed ventral spinal nerve roots is, of course, no guarantee that man can do likewise. However, since the general frustration of axonal regeneration in the central nervous system does not apply to fibers growing in the ventral rootlet tracts, and since the large impediment to regeneration of ventral spinal nerve roots is the impediment offered to regeneration anywhere in the peripheral nervous system, namely, mesodermal connective tissue, especially in scar formation, an open mind toward the possibility of regeneration of ventral roots in man, perhaps with surgical intervention to cope

3. Tower, S. S.: A Search for Trophic Influence of Posterior Spinal Roots on Skeletal Muscle, with a Note on the Nerve Fibers Found in the Proximal Stumps of the Roots After Excision of the Root Ganglia, *Brain* **54**:99, 1931.

4. Jones, D. S.: Studies on the Origin of Sheath Cells and Sympathetic Ganglia in the Chick, *Anat. Rec.* **73**:343, 1939.

with scar tissue in the spinal canal, and with care for the musculature for the period of years that may be required for regrowth, might alter the now hopeless prognosis for this condition. With interest in the regenerative capacities of all parts of the nervous system, currently stimulated, on the one hand, by the intensified study of polionmyelitis and, on the other, by the war, these observations are offered to invite reexamination of the regenerative capacity of avulsed ventral spinal roots in man.

SUMMARY

Ventral spinal nerve roots were avulsed from the cord in 4 cats and the animals killed after periods of from four weeks to one year. Evidence of regeneration was sought during life and found in the longest-surviving animal. Reinnervation of the denervated skeletal muscle was demonstrated histologically in the 2 longest-surviving animals. Evidence of vigorous regeneration on the part of the ventral root fibers was observed either grossly at autopsy or on microscopic examination in all the animals, beginning deep in the rootlet tracts of the cord. The cells of the cord were variously affected, many being destroyed completely, others surviving. The assumption that ventral nerve roots cannot regenerate if avulsed from the cord is, therefore, obviously unfounded as a generality. The evidence invites reconsideration of the potential regenerative capacity of the ventral spinal roots after similar damage in man.

Department of Anatomy, Johns Hopkins Medical School.

STUDIES IN DISEASES OF MUSCLE

XI. PROGRESSIVE MUSCULAR ATROPHY: REPORT OF A CASE WITH UNUSUAL FEATURES; EFFECT OF PROSTIGMINE AND PHYSOSTIGMINE ON FASCICULATIONS; METABOLISM OF ASCORBIC ACID

A. T. MILHORAT, M.D.

AND

T. P. ALMY, M.D.

NEW YORK

The present paper may properly be considered as consisting of three parts: (1) report on a patient in whom the clinical picture was that of progressive chronic anterior poliomyelitis with onset of symptoms in earliest childhood and a course that had been slowly progressive for about twenty-six years; (2) investigations on the effect of prostigmine and physostigmine on muscular fasciculations in this patient and in other subjects with progressive muscular atrophy, with comparison of the effects on the adventitious movements and those on choline esterase activity, and (3) a study of the metabolism of ascorbic acid in this and in other patients after administration of large amounts of the vitamin for prolonged periods.

METHODS

During the period of investigation the patient was in the research metabolism ward of the New York Hospital, where the diet could be rigorously supervised. A creatinine-creatine-free diet constant in its content of calories, protein and ascorbic acid from day to day was given. All specimens of urine were collected in dark-colored bottles containing acetic acid and immediately placed in the refrigerator to preserve the vitamin. The specimens of each period of exactly twenty-four hours were mixed together and analyzed for amounts of preformed creatinine, creatine, total nitrogen and ascorbic acid by the methods discussed in earlier reports.¹

The name "fasciculations" is used in this report for the adventitious movements commonly seen in the muscles of patients with progressive disease of the anterior horn cells. These contractions usually are referred to as "fibrillations" in the clinical

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From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, *Arch. Neurol. & Psychiat.* **38**:992-1024 (Nov.) 1937. Milhorat, A. T.; Bartels, W. E., and Toscani, V.: Effect of Hepatic Injury on Vitamin C Excretion in Fasting Dogs, *Proc. Soc. Exper. Biol. & Med.* **45**:394-397, 1940.

literature, a designation that probably should be limited to the spontaneous fibrillar twitching that has its onset on the fourth or fifth day after denervation (Langley and Kato²) and can best be demonstrated by viewing the exposed surface of the muscle. When fibrillations are well developed, the muscle shows a continuously quivering surface. Usually these fibrillations cannot be demonstrated in patients by clinical examination. On the other hand, the spontaneous muscular contractions discussed in this report are visible through the skin and subcutaneous tissues. Denny-Brown and Pennybacker³ pointed out that the muscular elements involved are larger than a single muscle fiber and probably represent the fibers in a motor unit. Clark⁴ counted an average of about 120 muscle fibers in the motor unit of the soleus muscle of the cat. Denny-Brown and Pennybacker suggested the name "fasciculations," and it appears advisable to use the term to distinguish this type of contraction from the "fibrillations" discussed by Langley and Kato.

In a series of investigations the effect of prostigmine and physostigmine on the muscular fasciculations was observed. The procedure was as follows: During the morning, while the patient was lying comfortably in bed, careful note was made by simple inspection of the sites and amount of fasciculation. The patient was then given a subcutaneous injection of either prostigmine methylsulfate or physostigmine sulfate. Changes in fasciculations and any side effects, such as sweating, pallor, abdominal cramps, nausea and vomiting and changes in pulse rate, were recorded at various times. The choline esterase activity of the serum was determined before the administration of the drug and at different intervals after the injection, including the time when the effect of the drug was considered to be at its maximum. For the estimation of the choline esterase activity of the serum, the procedure previously discussed⁵ was used.

REPORT OF CASE

History.—An unmarried woman aged 28 was admitted to the New York Hospital on Sept. 23, 1940. Her birth and development during the first year of life were said to have been normal. She did not walk until the age of 2 years. The gait from the beginning was waddling, and there was lordosis. She was overweight until about the age of 8, when she lost weight steadily, and has since been very thin and underweight. During her earliest days in school it was noted that she was unable to hold a pencil in her hand in normal fashion. The hands were weak, and she appeared unable to use the thumb in writing. At about the same time the patient complained of weakness of the lower extremities, but despite this she was able to walk considerable distances to and from school. The disability progressed very slowly, but at the age of about 13 the weakness increased more rapidly. During the next three years the disability in the lower extremities had progressed to the point where she was unable to walk more than five blocks on level ground. The difficulty in using the hands likewise increased, and at the age of 16 the patient was unable to extend the fingers. At about the same time she noted numerous fasciculations of the muscles of the trunk and four extremities.

2. Langley, J. N., and Kato, T.: The Physiological Action of Physostigmine and Its Action on Denervated Skeletal Muscle, *J. Physiol.* **49**:410, 1915.

3. Denny-Brown, D. E., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, *Brain* **61**:311, 1938.

4. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, *Am. J. Physiol.* **96**:296-304, 1931.

5. Milhorat, A. T.: The Choline-Esterase Activity of the Blood Serum in Disease, *J. Clin. Investigation* **17**:649-657. 1938.

Muscular weakness and wasting progressed slowly but steadily from the age of 16 until about two years prior to the date of her admission to the hospital. During this two year period progression of weakness, especially of the lower extremities, was more rapid. At the time of her admission the patient complained of being able to walk only short distances, and then with difficulty, and of tiring easily when standing. She stated that she usually felt somewhat weaker during the

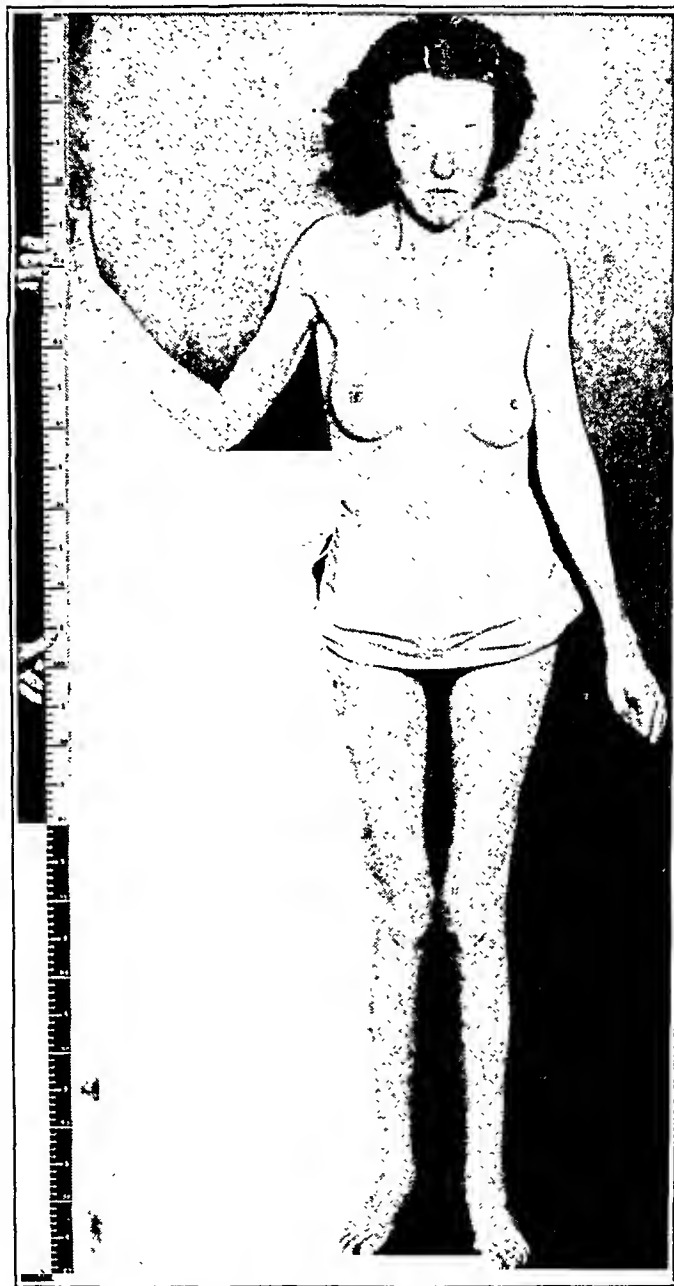


Fig. 1.—Photograph of patient with progressive muscular atrophy.

early hours of the day than in the afternoon. The rest of the history with reference to the nervous and muscular systems was negative. There was no record of a preceding febrile condition.

The familial history revealed no instance of similar illness or of any disease of the muscles or nervous system.

Examination.—The patient was thin and poorly nourished, with small wasted muscles, moderate dorsal scoliosis and considerable lordosis (fig. 1). Her gait

was slow and waddling. She had considerable difficulty in raising the trunk to a sitting position when in bed and was unable to assume the upright position without support. Practically all the muscles of the extremities and trunk showed reduction in volume and power. Muscular wasting was more evident in the peripheral portions of the extremities. The hands showed advanced wasting of the thenar and hypothenar eminences and of the interosseous muscles. The first interphalangeal joints of the fingers were ankylosed in the position of flexion. The hands presented a moderately advanced *main en griffe* appearance (fig. 2). The feet were flat and showed considerable wasting of the muscles. The patient was unable to move the feet against even slight passive resistance. All the tendon reflexes were absent. The plantar response was of flexor type bilaterally. Over the entire trunk and the four extremities numerous fasciculations were present. These were increased when the muscles were tapped with a percussion hammer. Sensibility for pain, light touch, vibration, position and temperature was intact. The peripheral nerve trunks were not enlarged or tender on palpation. The weight was 43 Kg.



Fig. 2.—Hand of patient with progressive muscular atrophy, whose photograph is shown in figure 1.

Laboratory Data.—The concentrations of urea nitrogen, nonprotein nitrogen, calcium and phosphorus in the blood were normal. Determinations of the prothrombin level of the blood, the urea clearance test for renal function and gastric analysis showed no abnormality. The activity of the choline esterase of the serum was 3 units (normal value); the phosphatase level was normal. The basal metabolic rates on four occasions were between $+3$ and $+6$ per cent. Two electrocardiograms were normal. Roentgenologic examination showed accentuation of the lumbosacral curvature of the spine and slight diffuse decalcification of the bones of the hands, spine and pelvis. The average daily urinary output of preformed creatinine and creatine was 0.700 and 0.200 Gm., respectively. The creatinine index (milligrams of preformed creatinine per kilogram of body weight) was 16. The creatine tolerance (retention of ingested creatine) was 33.5 per cent. Microscopic examination of a piece of a tissue removed from the left deltoid muscle showed

the fibers to be normal, except those in one small area, where they were in an early stage of necrosis. There was slight increase in the connective tissue.

Subsequent Course.—One and a half years later the patient reported that the muscular disability had progressed only slightly since she had left the hospital.

The clinical picture is typical of progressive muscular atrophy resulting from disease of the anterior horn cells. However, the onset during the first five years of life and the long course are most unusual, since progressive muscular atrophy of this type almost always begins between the ages of 25 and 55 and usually terminates fatally in from two to five years. In cases of progressive muscular atrophy of the Charcot-Marie-Tooth peroneal type, an early age of onset is not unusual, and a course of many years' duration is common; however, the absence of even minor defects in sensibility, the extent and activity of fasciculations and the apparently simultaneous involvement of all four extremities at so early an age as that of this patient are features making this diagnosis less likely. Any of these phenomena can occur in certain cases of progressive peroneal muscular atrophy, but their concomitant appearance in a patient with considerable lordosis is unusual for this disease. The negative familial history apparently is of little significance in making the diagnosis. Whereas many patients with progressive peroneal muscular atrophy give a history of some other person in the family with the disease, perhaps an equal number give a negative familial history.

A diagnosis of peripheral neuritis is not justified in this case because of the absence of all subjective and objective involvement of sensibility. Progressive muscular dystrophy, in rare instances, can begin in peripheral groups of muscles, but the number and character of the fasciculations in this case make such a diagnosis unlikely. Moreover, microscopic examination of the piece of muscle removed for biopsy revealed changes more commonly seen in muscles wasted as a result of disease of the anterior horns than in muscles with progressive dystrophy. In cases of the former condition Slauck⁶ observed small groups of muscle fibers in different stages of atrophy surrounded by entirely normal fibers, whereas in cases of progressive muscular dystrophy the atrophic and normal fibers were seen lying side by side without the arrangement observed in disease of the anterior horn cells.

From the point of view of diagnosis of any of the muscular syndromes, this case presents many extraordinary features. We never have seen another case with these characteristics and have been unable to find a report of a similar case in an extensive survey of the literature.

6. Slauck, A.: Beiträge zur Kenntnis der Muskelpathologie, Ztschr. f. d. ges. Neurol. u. Psychiat. **71**:352-356, 1921.

EFFECT OF PROSTIGMINE AND PHYSOSTIGMINE ON FASCICULATIONS

The accompanying table gives a summary of the data observed on this patient. It will be noted that both prostigmine and physostigmine increased muscular fasciculations, but that prostigmine had considerably more effect on skeletal muscles and less effect on other organs than had physostigmine. These differences occurred even when the drugs were given in amounts that decreased the choline esterase activity of the serum to similar levels. Significant increase in muscular fasciculations accompanied only slight changes in esterase activity after prostigmine had been given, whereas similar changes in esterase activity induced by physostigmine were without effect on the fasciculations. Similar investigations made on 4 other patients with muscular atrophy subsequent to disease of the spinal cord gave the same results. Moreover, prostigmine produced fasciculations in muscles in which no adventitious movements previously had been observed. For example, numerous fasciculations were

Effect of Prostigmine Methylsulfate and Physostigmine Sulfate on Muscular Fasciculations

Serum Esterase Activity, Units		Muscular Effects *	Side Effects †	Drug, Mg.
Resting Level	Level After Drug			
3.02	2.60	+++	—	Prostigmine methyl sulfate, 0.5
2.91	1.95	++++	—	Prostigmine methyl sulfate, 1.0
3.01	2.27	—	—	Physostigmine sulfate, 0.6
2.93	1.98	+	+++	Physostigmine sulfate 1.2

* Increase in fasciculations.

† Dizziness, sweating, nausea and abdominal cramps.

regularly produced in the face and tongue by prostigmine, although these were never seen when the patient had not been given the drug.

Physostigmine often induced side effects even in doses that had little effect on fasciculations. The administration of prostigmine was followed by side effects only when large doses were given and considerable increase in fasciculations was produced. The side effects of either drug were abolished readily by atropine. On the other hand, the effect on fasciculations appeared to be uninfluenced by atropine. Furthermore, atropine was without effect on the spontaneous adventitious movements. Langley and Kato,² in their studies on denervated muscle, expressed the belief that physostigmine had both a central and a peripheral action and that atropine opposed the former but did not affect the latter. Russel, Odom and McEachern⁷ found atropine to be without influence either on the fasciculations produced by prostigmine in animals or on the effect of prostigmine on fasciculations occurring in patients with

7. Russel, C. K.; Odom, G., and McEachern, D.: Physiological and Chemical Studies of Neuromuscular Disorders, Tr. Am. Neurol. A. **64**:120-124, 1938.

progressive muscular atrophy. Denny-Brown and Pennybacker⁸ expressed the opinion that fasciculations in progressive muscular atrophy may be the result of intermittent discharges from the diseased motor neurons. However, the peripheral origin of fasciculations in this disease is suggested by their persistence after spinal anesthesia⁹ or blocking of the peripheral nerve by procaine.⁹ It appears that the two views can be reconciled by the formulation that the slowly degenerating muscle fibers are abnormally sensitive to stimulation and that the involuntary impulses increase the fasciculations. Increased sensitivity of the muscles in progressive muscular atrophy is shown by the observation recorded here, namely, that amounts of prostigmine that are without effect in normal subjects can induce fasciculations in muscles in which no adventitious movements had previously been seen. These effects of prostigmine and physostigmine on fasciculations cannot be explained entirely by the inhibitory effect on the choline esterase activity. The situation is analogous to that seen in cases of myasthenia gravis, in which prostigmine has greater muscular effects than has physostigmine even when the changes in choline esterase activity induced by the two drugs are similar.¹⁰ It is likely that the effects of the drugs on fasciculations in progressive muscular atrophy and on muscular function in myasthenia gravis are due partly to their antiesterase action and partly to direct action on the muscle.

METABOLISM OF ASCORBIC ACID

The urinary output of ascorbic acid was determined daily for two months. During a period in which the patient was given a creatinine-creatine-free diet containing about 50 mg. of the vitamin the average daily excretion was 26 mg. The addition of 500 mg. of crystalline ascorbic acid to the diet increased the output to around 115 mg. On days when 500 mg. of the vitamin was given subcutaneously in place of a dietary supplement of similar amounts the output was unchanged. An increase in the dietary supplements of ascorbic acid to 700 mg. (500 mg. of crystalline ascorbic acid and 200 mg. in tomato juice) induced only a slight rise in the daily output, namely to a level of 130 mg. The amounts of the vitamin in the urine represented only 16 per cent of the

8. Grund, G.: Ueber Bewegungsvorgänge des menschlichen quergestreiften Muskels, die von der motorischen Vorderhornanglienzelle unabhängig sind. Beitrag zur Pathologie rheumatischer Krankheitszustände, Deutsche med. Wchnschr. **64**: 488, 1938; Ueber die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, Deutsche Ztschr. f. Nervenhe. **145**:99-109, 1937.

9. de Jong, H., and Simons, D. J.: A Comparative Study of Fibrillation and Tremor, J. A. M. A. **118**:702-705 (Feb. 28) 1942. Russel, Odom and McEachern.⁷

10. Milhorat, A. T.: Studies in Diseases of Muscle: X. Prostigmine and Physostigmine in the Treatment of Myasthenia Gravis, Arch. Neurol. & Psychiat. **46**:800-834 (Nov.) 1941.

amount ingested. On days when a total of 825 mg. of ascorbic acid was given (200 mg. subcutaneously, 500 mg. orally and 125 mg. in tomato juice) an average of 150 mg. was excreted (17 per cent). During the period when the 500 mg. of the vitamin was given daily the amount of ascorbic acid in the plasma was 0.5 mg. per hundred cubic centimeters (normal values are from 0.7 to 1.4 mg.); when 700 mg. was given the amount in the plasma was 0.9 mg. per hundred cubic centimeters.

The urinary excretion of ascorbic acid was studied in 7 other patients to whom large doses of the vitamin were given. Three patients with progressive muscular dystrophy, 1 patient with Friedreich's disease and 1 subject with limited muscular wasting subsequent to an acute attack of anterior poliomyelitis fifteen years previously, who were given from 400 to 500 mg. of ascorbic acid daily for periods of several weeks, excreted from 60 to 90 per cent of the vitamin. When similar amounts of the vitamin were given to another patient with extensive muscular wasting due to chronic progressive anterior poliomyelitis and 1 patient with dermatomyositis and severe Raynaud's syndrome, only about 20 per cent of the administered dose was excreted.

The data make it improbable that the low urinary output can be ascribed to abnormal absorption from the intestine, impaired function of the kidneys or previous deficiency of the vitamin. The excretion was unchanged by parenteral administration of the vitamin; tests of renal function were normal, and the output did not increase even after a period of two months, during which at least 500 mg. of ascorbic acid was given daily. It is of interest that the other patient with progressive muscular atrophy subsequent to disease of the anterior horn cells likewise excreted small amounts of the vitamin while receiving a large amount. The third patient showing a low urinary output had extensive muscular involvement with severe Raynaud's disease. The factors determining the low urinary output of ascorbic acid of these 3 patients are not known. The excretion of the vitamin by the other 5 patients in this series was similar to that observed by Storvick and Hauck¹¹ for normal subjects receiving large amounts of ascorbic acid.

The low excretion of ascorbic acid by the 3 patients was unexpected, since the original objective of the study was the effect of the vitamin on creatinuria. Hirata and Suzuki¹² reported diminution in the output of creatine in cases of progressive muscular dystrophy when amounts of from 200 to 500 mg. of ascorbic acid were administered daily for periods of about two weeks. However, in all 8 patients in the present

11. Storvick, C. A., and Hauck, H. M.: Effect of Controlled Ascorbic Acid Ingestion upon Urinary Excretion and Plasma Concentration of Ascorbic Acid in Normal Adults, *J. Nutrition* **23**:111-123, 1942.

12. Hirata, Y., and Suzuki, K.: A New Information Concerning Progressive Muscular Atrophy and Vitamin-C, *Orient. J. Dis. Infants* **18**:83, 1935; *Dystrophia Musculorum Progressiva und Vitamin C*, *Klin. Wchnschr.* **16**:1019, 1937.

series ascorbic acid was without effect on the daily excretion of creatine and creatinine. It is difficult to explain the results of Hirata and Suzuki, but it appears that other factors still unrecognized may have played a significant role in their investigations. Thus, Milhorat, Weber and Toscani¹³ observed a definite decrease in the excretion of creatine in 2 patients with dermatomyositis when large amounts of wheat germ and ascorbic acid were given, whereas ascorbic acid alone was without effect. Similar results were observed by Milhorat and Toscani¹⁴ in a patient with progressive muscular dystrophy. Whether the patients of Hirata and Suzuki suffered from previous deficiency of ascorbic acid or whether substances similar to those present in wheat germ unknowingly were given together with the vitamin cannot be stated at this time. While ascorbic acid appears to be without value in the treatment of the muscular diseases,¹⁵ there is evidence that the metabolism of the vitamin is related significantly to that of creatine (Milhorat, Hardy, Bartels and Toscani¹⁶).

SUMMARY

The case history of an adult with progressive muscular atrophy is presented. The features were typical of chronic anterior poliomyelitis, with the unusual feature of onset of disability in infancy.

Prostigmine and physostigmine increased the fasciculations in this patient and in other subjects with progressive muscular atrophy. Prostigmine had greater effects on fasciculations than had physostigmine even when the inhibitory effect on choline esterase activity of the serum was the same. It is postulated that the effect on fasciculations is due only partly to the antiesterase activity of the drugs and that these drugs have a direct action on skeletal muscle. In addition to increasing fasciculations in areas where they already are active, prostigmine and physostigmine may induce fasciculations in areas previously free of them, even when the drugs are given in doses that are without effect in normal subjects.

Two patients with progressive muscular atrophy who received large amounts of ascorbic acid excreted in the urine an abnormally low percentage of the administered vitamin.

525 East Sixty-Eighth Street.

13. Milhorat, A. T.; Weber, F. C., and Toscani, V.: Metabolic Studies in Dermatomyositis, with a Note on the Effect of Wheat Germ, *Proc. Soc. Exper. Biol. & Med.* **43**:470-473, 1940.

14. Milhorat, A. T., and Toscani, V.: Unpublished data.

15. Milhorat, A. T.: Treatment of Diseases of Muscle, New York State J. Med., to be published.

16. Milhorat, A. T.; Hardy, J. D.; Bartels, W. E., and Toscani, V.: Effect of Shivering, Iodoacetate, and Epinephrine on Vitamin C and Creatine Excretion in Fasting Dogs, *Proc. Soc. Exper. Biol. & Med.* **45**:397-399, 1940.

FASCICULAR MUSCLE TWITCHINGS IN AMYOTROPHIC LATERAL SCLEROSIS

THEIR ORIGIN

ROY LAVER SWANK, M.D., PH.D.*

AND

JERRY C. PRICE, M.D.

Assistant Neurologist, Neurological Institute of New York
NEW YORK

Grund¹ and later Shelden and Woltman² found that the intrathecal injection of procaine in an amount sufficient to produce complete motor paralysis of the legs did not abolish the muscular fibrillations in patients with amyotrophic lateral sclerosis. These experiments were interpreted as showing that the impulses causing these fibrillations did not arise from the cell bodies of the motor neurons of the ventral horn. Each of these investigations consisted of but 1 experiment; the nature of the muscular twitchings was not controlled by electrical recordings, and no further attempt was made to locate the source of the impulses causing the fibrillations. For these reasons the present study was undertaken.

PROCEDURE

Three patients with typical and advanced amyotrophic lateral sclerosis and 2 others with progressive muscular atrophy with muscular fibrillation³ were utilized in this study. Three of the patients exhibited many and 2 relatively infrequent muscular fibrillations at the time they were studied.

The muscular fibrillations were observed clinically, and their action potentials were picked up by microelectrodes, amplified by a Grass condenser-coupled amplifier and recorded by ink writers.

To produce paralysis of individual or groups of muscles, a 1 or 2 per cent solution of procaine hydrochloride was injected directly into the nerve supply, or

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* A Commonwealth Fund Fellow. Dr. Swank is now serving as captain in the Medical Corps of the United States Army.

From the Department of Medicine, Harvard Medical School, and the Medical Clinic of the Peter Bent Brigham Hospital, Boston, and the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

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200 mg. of procaine hydrochloride crystals dissolved in 2 cc. of spinal fluid was injected intrathecally. In 2 instances the degree of paralysis was checked by stimulating the nerve above the point of procainization with a faradic current furnished by a Harvard inductorium. Currents as strong as the patient could tolerate did not produce a response in the muscle at a time when paralysis of voluntary effort was complete.

RESULTS

A. Spinal Anesthesia.—Spinal anesthesia was produced in 2 patients. In 1 of these patients fibrillations, which were numerous in most of the muscles of the lower extremities before anesthesia appeared to be greatly reduced in number. In the figure, 1 is a control record from the medial portion of the rectus femoris muscle just above the knee; 2 was taken from the same muscle and 3, from the peroneus longus muscle after spinal anesthesia had produced complete paralysis of the lower extremities. These records indicate that the spinal anesthesia had reduced fibrillations 50 to 65 per cent quantitatively, the nature of their action potentials remaining essentially unchanged. In a second patient complete motor paralysis was produced in the same way, with similar results.

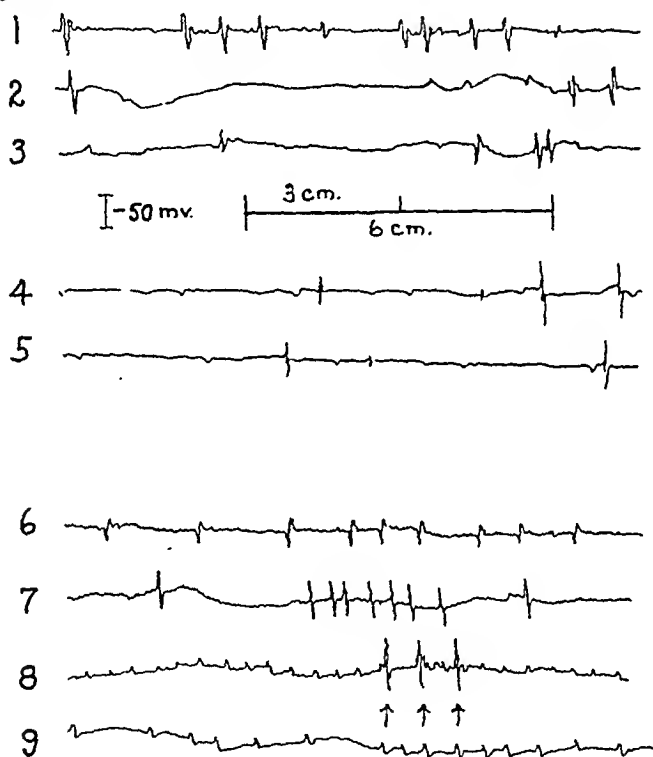
B. Peroneal (Anterior Tibial) Nerve.—In 5 experiments (3 patients) procaine was injected at the point where the nerve passes lateral to the fibula. The injection was followed by complete paralysis of the dorsal flexor muscles of the foot in each patient. In 1 of these patients (2 experiments) the fibrillations, which were numerous, were completely abolished by this procedure. In the other 2 patients (3 experiments) the fibrillations, which were infrequent during the control period, were but slightly decreased in number. In 1 of the latter 2 patients fibrillations were abolished subsequently by injecting procaine directly into the muscle in a line about 4 cm. above the recording electrode. In the other patient it was necessary to inject procaine into the muscle 2 cm. above the recording electrode to produce a pronounced reduction in fibrillations, and only after the procaine had been injected directly into the fibrillating muscle were the twitchings abolished. Tracing 4 is a control record from the anterior tibial muscle in the first of the latter 2 patients. Tracing 5 was recorded from the same muscle after foot drop was produced by injection into the peroneal nerve at the fibula. Immediately after this procaine was injected into the muscle about 4 cm. above the electrode, after which no action potentials were recorded.

C. Ulnar Nerve.—Procaine was injected into the ulnar nerve at the elbow, with the production of complete paralysis of the hypothenar muscles in 3 experiments (1 patient). This procedure reduced the number of visible fibrillations, but did not abolish them entirely. In each of these experiments subsequent injection into the ulnar nerve at the wrist abolished all visible fibrillations. Tracing 6 is a record of the action potentials produced by fibrillary twitchings in the hypothenar muscles during the control period. Tracing 7 shows a burst of similar potentials after injection into the ulnar nerve at the elbow. Occasionally

much smaller action potentials, not accompanied by visible muscular fibrillations, were observed after this injection. These are shown in 8, three much larger potentials accompanied by visible fibrillations being indicated by arrows. After injection into the ulnar nerve at the wrist occasional bursts of the very small action potentials not accompanied by visible fibrillations were still seen (tracing 9), both spontaneously and after manipulation of the little finger.

D. General Observations.—Stretching and then relaxing a muscle frequently produced bursts of fibrillations. Also any body movement, for

Figures



In this figure, 1, 2 and 3 are records of action potentials produced by fibrillating muscle bundles in the lower extremities before (1) and after (2 and 3) spinal anesthesia. The paper speed was 6 cm. per second.

Tracings 4 and 5 are records of action potentials produced by fibrillating muscle bundles in the anterior tibial muscle before (4) and after (5) the injection of procaine hydrochloride into the peroneal nerve lateral to the fibula. The paper speed was 3 cm. per second.

Tracings 6, 7, 8 and 9 are records of action potentials produced by fibrillating muscle bundles in the hypotenar muscles before (6) and after (7 and 8) injection of procaine hydrochloride into the ulnar nerve at the elbow and at the wrist (9). The paper speed was 6 cm. per second.

example, hyperventilation or waving the arms, increased or brought out fibrillations in muscles being studied even though they remained at rest.

For these reasons great care was necessary to insure that the conditions under which the action potentials were studied varied as little as possible. Prostigmine methylsulfate injected subcutaneously appeared to increase the number of fibrillations. After procainization of the nerve supply to the muscle prostigmine did not cause the fibrillations to reappear.

COMMENT

In the discussion which follows it is assumed that the injection of procaine into a peripheral nerve, as performed in these experiments, blocks completely the passage of stimuli in the motor nerve fiber.

Apparently, in patients with amyotrophic lateral sclerosis, the stimuli which cause the muscular fasciculations can have their origin in a peripheral nerve fiber independent of its cell body. Probably the cell body can also originate these stimuli, since in 2 patients the fibrillations, which were many, were reduced approximately 50 per cent by spinal anesthesia. However, the stimuli causing them may have arisen from the peripheral nerve process adjacent to the cell body, rather than from the cell body itself. In 2 other patients with relatively few fibrillations nearly all of these stimuli appeared to arise from the distal part of the peripheral nerve process, since blocking the nerve with procaine a few centimeters above its termination only slightly altered the fibrillations (figure, 4 and 5).

In another study³ it was suggested that the presence of many fibrillations in a patient with amyotrophic lateral sclerosis indicated rapidly progressive, and few fibrillations slowly progressive, amyotrophy. According to our studies, in cases of the rapidly progressive type a large part of the neuron, especially its distal portion, appears to be affected, whereas in cases of the latter, or slowly progressive, type the disturbance appears to be limited to or especially marked near the termination of the nerve fiber. This indicates that the functional impairment in the lower motor neuron in these cases develops near its termination first and progresses centralward. Perhaps the ultimate degeneration is of the same type as that seen with thiamine deficiency.⁴ Pathologic⁵ and clinical³ studies suggest that the degeneration in the pyramidal tracts is also retrograde in patients with amyotrophic lateral sclerosis.

The nature of the change in the peripheral nerves which provokes these uncontrollable stimuli is not clear. There seems to be an element of increased irritability, which is supported by the presence of a definitely

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lowered chronaxia early in the disease.⁶ Many of the observations of Denny-Brown and Pennybacker⁷ suggest the same origin. Perhaps "spilling over" of some substance which normally gives rise to these stimuli or products of abnormal metabolism in the neuron are capable of provoking them.

Although the number of action potentials was reduced, their amplitude was not notably changed by spinal anesthesia. However, in 2 experiments in which the ulnar nerve was blocked at the elbow and wrist, and in 1 instance in which the peroneal nerve was blocked at the fibula, many low amplitude potentials, not accompanied by visible fibrillations, appeared in the record (figure, 8 and 9). It is possible that these low amplitude potentials were produced by contracting muscle groups at some distance from the electrode, although this seems unlikely, as they were not present before anesthesia. An alternative explanation is suggested by the fact that a single motor nerve fiber must bifurcate many times before its termination in order to innervate as many as one hundred and sixty-five muscle fibers,⁸ the motor neuron unit. It is known that many of these bifurcations occur in the peripheral nerve.⁹ Stimuli arising independently in a subdivision of the main nerve fiber could cause a part of the motor neuron unit to contract and produce the smaller action potentials. The nerve block central to this point would prevent a motor unit response from a stimulus originating proximally or spread of the stimulus to the entire unit. The weakness of the contraction would prevent it from being visible through the skin.

CONCLUSIONS

The stimuli provoking fascicular twitchings which appear in the muscles of patients with amyotrophic lateral sclerosis appear to be derived mainly from peripheral motor nerve fibers. In patients with numerous fibrillations these stimuli seem to arise from the entire nerve process and probably also to a less extent from the cell body. In other patients, with few fibrillations, the stimuli appear to arise almost entirely from near or at the termination of the nerve fibers.

Fifth General Hospital, United States Army, A. P. O. 1001, care of Postmaster.

Neurological Institute of New York.

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FAMILIAL TYPE OF PARALYSIS IN INFANTS AND ITS RELATIONSHIP TO OTHER HEREDOFAMILIAL DISORDERS

A CLINICOPATHOLOGIC STUDY

ALBERT J. LUBIN, M.D.*
SAN FRANCISCO

OTTO MARBURG, M.D.
NEW YORK
AND

K. TAMAKI, M.D.
SAN FRANCISCO

In spite of the clear differentiation between various heredofamilial neurologic syndromes, many instances of transitional forms have been described from both the clinical and the pathologic viewpoint, particularly among the syndromes of Friedreich's ataxia, Marie's heredocerebellar ataxia, Charcot-Marie-Tooth peroneal muscular atrophy, hereditary spastic paralysis and Leber's hereditary optic nerve atrophy. This report concerns a disease occurring in 3 siblings which does not easily fall under any previously described disease entity. Clinically the condition in 1 case resembled infantile progressive spinal atrophy (Werdnig-Hoffmann disease). Histopathologically it was related to amaurotic family idiocy (Tay-Sachs disease) but presented changes that are also seen in other, supposedly unrelated, forms of heredofamilial disorder.

REPORT OF CASES

The 3 cases occurred in a family in which no previous nervous disorder was known. Both parents were born in Ireland, of Irish stock. During the course of twenty years the mother had been pregnant fourteen times, eleven of the pregnancies terminating in full term deliveries and three in miscarriages. Three of the eleven children, the fourth, seventh and eleventh (fig. 1), were afflicted with the disease. All of the others are living and well except the second, who died at the age of 6 weeks of "inflammation of the bowel." The report of the first case was obtained from the University of California Hospital; the second, from the Children's Hospital of Oakland, Calif., and the third case was studied in the department of pediatrics of the Stanford University School of Medicine.

* Fellow of the Rockefeller Foundation.

From the Neurological Institute of New York, the Department of Neurology of Columbia University College of Physicians and Surgeons and the Division of Neuropsychiatry of the Stanford University School of Medicine.

CASE 1.—The child, a boy, was delivered normally. After a gastrointestinal upset at the age of 6 months, he was said not to be “as active as other children of his age.” Otherwise, as far as can be ascertained, his development was normal until he was 17 months old, when his neck was noted to be weak. After an attack of bronchitis, at the age of 19 months, he rapidly became weaker and was unable to hold up his head or bear his weight on his legs. He lost the ability to use the few words that he previously had learned and had difficulty in swallowing. He seemed able to recognize his parents. Physical examination at the age of 20 months revealed that the child was fairly well developed; nothing abnormal was noted except in the neurologic examination. Convergent strabismus of both eyes was present; the optic disks were somewhat pale, perhaps indicating incipient optic nerve atrophy. The pupils reacted to light. The radial, knee and ankle jerks were all elicitable. No pathologic reflexes were noted. The superficial reflexes were not obtained. The child was rated an imbecile in an intelligence test. He died at the age of 24 months, probably of bronchopneumonia.

CASE 2.—This child, a girl, was born three years after the first patient. She was seen at regular intervals in an outpatient clinic and by visiting nurses and was regarded as normal during the first year of life. Her only illnesses were

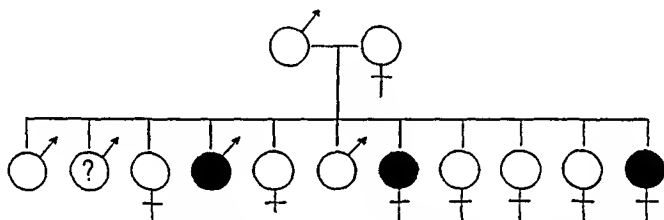


Fig. 1.—Familial distribution of cases. Offspring are shown in the order of birth. The black circles indicate affected offspring; the hollow circles, healthy children.

attacks of measles and pertussis. At the age of 13 months a visiting nurse remarked that the child seemed in good condition except that she could not yet stand and “seemed too heavy for her feet.” A month later the clinic physician made the following note: “The baby appears well nourished. Examination reveals essentially nothing of significance except for retarded physical development. She is probably normal mentally.” At the age of 15 months she was able to sit up for an hour at a time but still was unable to stand by herself. At 20 months there appeared attacks of cyanosis, labored respiration and “spasms.” Her intelligence was regarded as below that of the other members of the family at this age. Physical examination at 21 months of age showed the child to be well nourished and able to sit up for short periods. Strabismus was present; the pupils reacted well to light. The musculature seemed soft and flabby. The patellar, biceps and superficial abdominal reflexes were not obtained. The Wassermann reaction of the blood was negative. The only remarkable laboratory observation was a leukocyte count of 32,600 (polymorphonuclear leukocytes, 84 per cent; lymphocytes, 16 per cent). During the next four months the child became unable to move either her arms or her legs, and the “spasms” continued. She died of bronchopneumonia at the age of 24 months.

CASE 3.—This child, a girl, was born ten years after the patient in the preceding case. The mother felt the child was "not right" from the age of 7 months; the clinic physicians, however, could detect nothing remarkable at this time. At the age of 13 months it was believed that her physical development was retarded. The psychologist's report on a mental rating stated: "The child is slightly retarded. She is 14 months old and does the things expected of a child 1 year old and probably some more, but the examiner was strange and so could not get the most from her." At the age of 16 months, although able to crawl, she could not walk. During the following four months the child's condition became progressively worse. She lost the ability to crawl and remained in a supine position almost constantly. She did, however, reach for objects and play with things in her hands. She was able to flex her legs on her abdomen but seemed perfectly limp when placed on her feet. She was also observed to have a number of attacks, each lasting a few seconds, in which she became quiet, her pupils dilated and her face was "fixed, with a dull, staring look in her eyes." There was no motor seizure. She began to have difficulty in swallowing at the age of 19 months and became unable to speak. Three days before her death she often seemed fairly observant, while at other times she appeared to be unaware of her surroundings. She cried only with great effort and then produced but little noise. Physical examination at this time revealed the following condition: Right internal strabismus was present; the pupils reacted to light and in accommodation. The liver and spleen were not palpable. There was pronounced lumbar kyphosis. The extremities seemed completely relaxed, and the musculature was weak and flabby. She was able to hold objects in her hands, raise her arms up to her abdomen and move her toes slightly. There was flaccid paralysis of all other movements of the extremities. The knee jerks, although present, were difficult to elicit. The superficial abdominal reflexes were absent. Some fibrillations were noted in the muscles of the feet. Examination of the blood and urine revealed nothing of importance. She died at the age of 23 months; shortly before death she experienced difficulty in breathing, and her temperature rose to 42 C. (107.6 F.).

In all 3 cases the onset was first noted at about the first birthday, and death resulted near the second. A flaccid type of paralysis, involving especially the trunk and the proximal portions of the extremities, was present; the lower extremities appeared to be more seriously involved than the upper. The tendon reflexes were active in the first case, absent in the second and sluggish in the third. The musculature was flabby in all 3 cases, but no definite atrophy was detected. Fibrillations in the feet were noted in the third case. Mental impairment probably existed, though in varying degrees, in all the cases. This was an outspoken manifestation, however, only in case 1 (in which the child was rated as an imbecile). Seizures were observed in the second and third cases. Blindness was not apparent in any of the cases, although a possible beginning optic nerve atrophy was observed in the first. In case 3 the child was able to grasp for objects shortly before death. Strabismus was noted in each case.

The clinical diagnosis in these cases was difficult. The signs and symptoms, however, approached those of infantile amaurotic family

idiocy (Tay-Sachs disease), as well as those of infantile progressive muscular atrophy (Werdnig-Hoffmann disease), both familial disorders with an invariably fatal outcome. In no case was the cherry red spot characteristic of the former disease observed in the macula. In other respects the first case resembled Tay-Sachs disease: progressive paralysis with retention of tendon reflexes, mental deterioration and questionable beginning optic nerve atrophy. In the second and third cases no pronounced degree of mental impairment and no abnormal visual signs, except strabismus, were noted. Seizures, observed in both these cases, have been reported in association with Tay-Sachs disease. In spite of this, however, these cases were thought to be instances of infantile progressive muscular atrophy, inasmuch as the outstanding difficulty was flaccid paralysis with absent or sluggish tendon jerks. While atrophy was impossible to detect because of the abundant layer of subcutaneous fat, fibrillations and diminished reaction to faradic current were observed in 1 of the cases.

Postmortem Examination in Case 3.—Gross Description: The musculature of the back and abdomen appeared to be poorly developed, the latter being covered by a 2 cm. layer of subcutaneous fat. Under a similar thick layer of fat in the region of the calves, the muscles were severely atrophied. Aside from congestion in both lungs, nothing remarkable was noted in the viscera. Macroscopic examination of the nervous system revealed nothing abnormal except for the small size of the cerebellum.

Microscopic Examination of the Nervous System: The following staining methods were employed: hematoxylin and eosin, phosphotungstic acid hematoxylin, cresyl violet, Nile blue, scarlet red, Schaffer's modification of the Pal-Weigert technic and the methods of Bielschowsky, Mallory, Cajal and Kanzler.

Spinal Cord: The cellular changes (fig. 2) were similar at all levels of the cord. These changes were noted in all the cell columns but were especially noticeable in the nucleus dorsalis (Clarke's column) and in the cells of the posterior horn. Many of the cells were swollen. Some of the cell bodies had become rounded or pear shaped, while others retained a nearly normal form. Some appeared to be round and homogeneous, staining deeply with a variety of methods. The Nissl substance had disappeared completely in some cells and partially in others; in still other cells, especially those of the anterior horn, it seemed to be normal. In sections stained by the Bielschowsky method, the neurofibrils, while appearing to be distributed normally in some cells, were often pushed to the periphery and replaced by a granular cytoplasm, or a network of thick fibrils was seen inside the cell body. With the myelin stain many of the cells were observed to contain hematoxylinophilic granules (prelipoids). No neutral fat was present in the ganglion cells. The nuclei tended to be least affected. Some were located in the central portion of the cell body; however, in many of the seriously involved cells the nucleus was displaced to the periphery or pushed into the base of the swollen dendrite or had completely disappeared. Numerous cells were devoid of processes. In others, however, an irregular swelling of the process was seen, similar to the swelling of the cell. Some of the cells were indistinguishable from the type seen in axonal degeneration. Frequent shadow cells were scattered throughout the nuclear masses. Shrunken pyknotic cells were also observed.

Demyelination of both the lateral and the ventral corticospinal tract occurred throughout their entire course (fig. 3). The posterior column was involved in the thoracic and cervical regions. In the thoracic region an area corresponding to the medial root zone of Flechsig was involved; in the cervical region the fasciculus gracilis and the adjacent portions of the fasciculus cuneatus were affected.

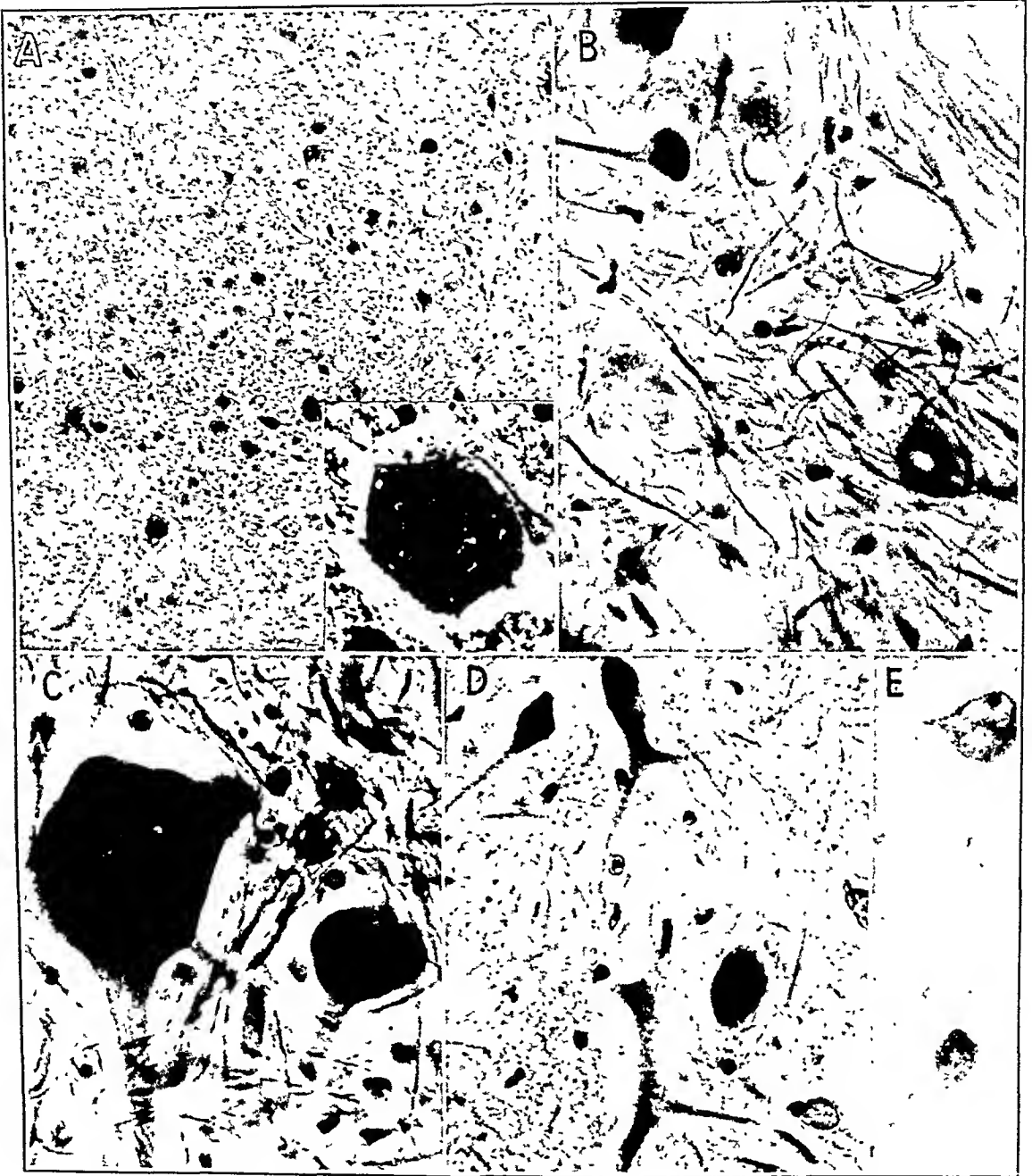


Fig. 2.—Cellular alterations in the spinal cord and medulla. *A*, large, rounded, amorphous cells in the posterior horn; cresyl violet stain. High power view in inset, stained by Bielschowsky method. *B*, mulberry body, shadow cell, empty cell space and shrunken pyknotic cell in the medulla; Bielschowsky stain. *C*, pear-shaped cells in the anterior horn; Bielschowsky stain. *D*, swollen dendrite, pyknotic cells and bloated glia cell in the anterior horn; cresyl violet stain. *E*, cell showing axonal reaction and shadow cell; cresyl violet stain.

The small oval area of Flechsig, composed of descending fibers, was the only afferent pathway involved below the thoracic region.

An increase in number of all types of glia cells was noted throughout the cord and was most evident in the posterior horn and in the area of the lateral

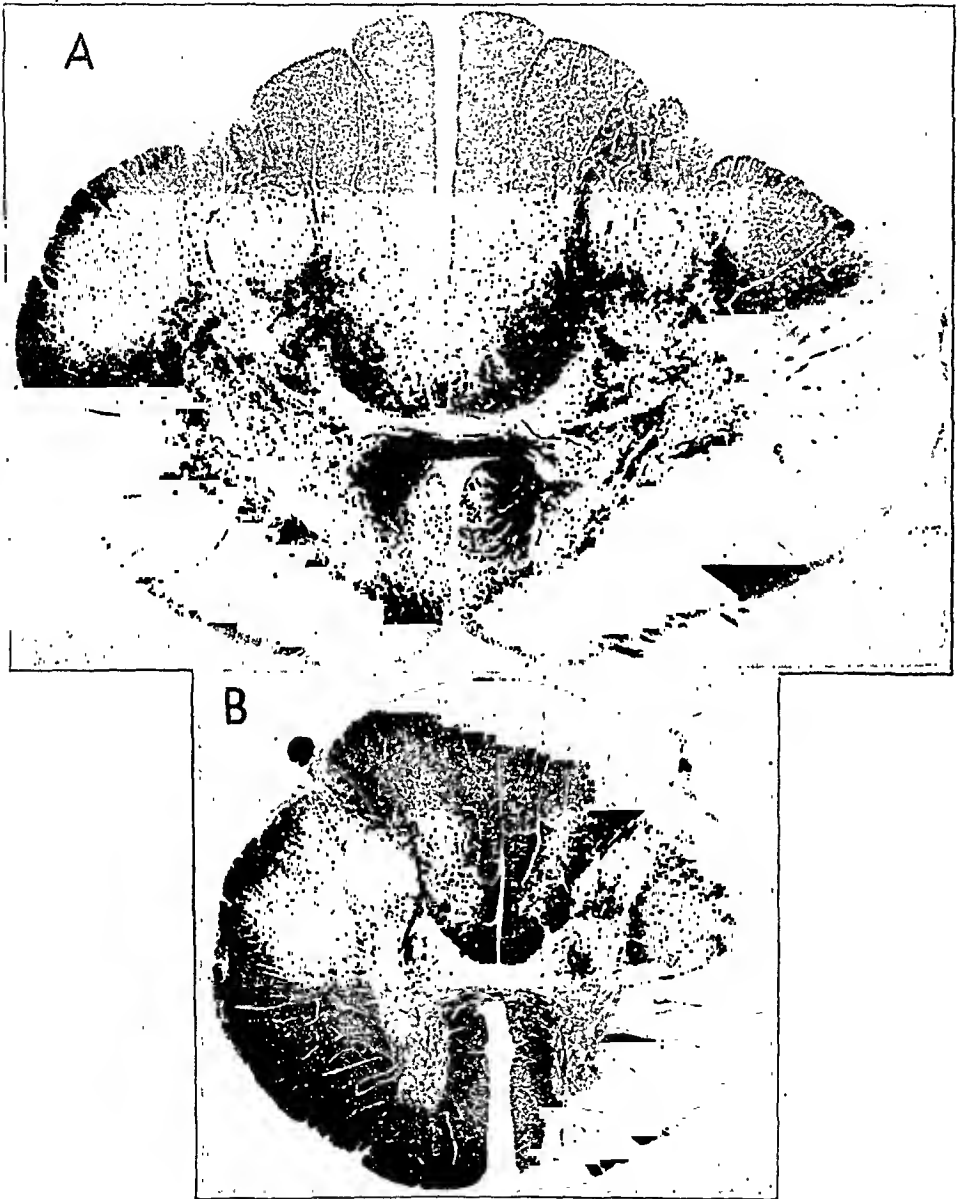


Fig. 3.—Demyelination in the lateral and ventral corticospinal tracts and in the posterior funiculus. In the cervical region (*A*) the demyelination of the posterior funiculus is most evident in the fasciculus gracilis, and in the thoracic region (*B*), in the area corresponding to the middle root zone of Flechsig. Myelin sheath stain.

corticospinal tract (fig. 4). Many swollen astrocytes and fat-laden gitter cells were seen.

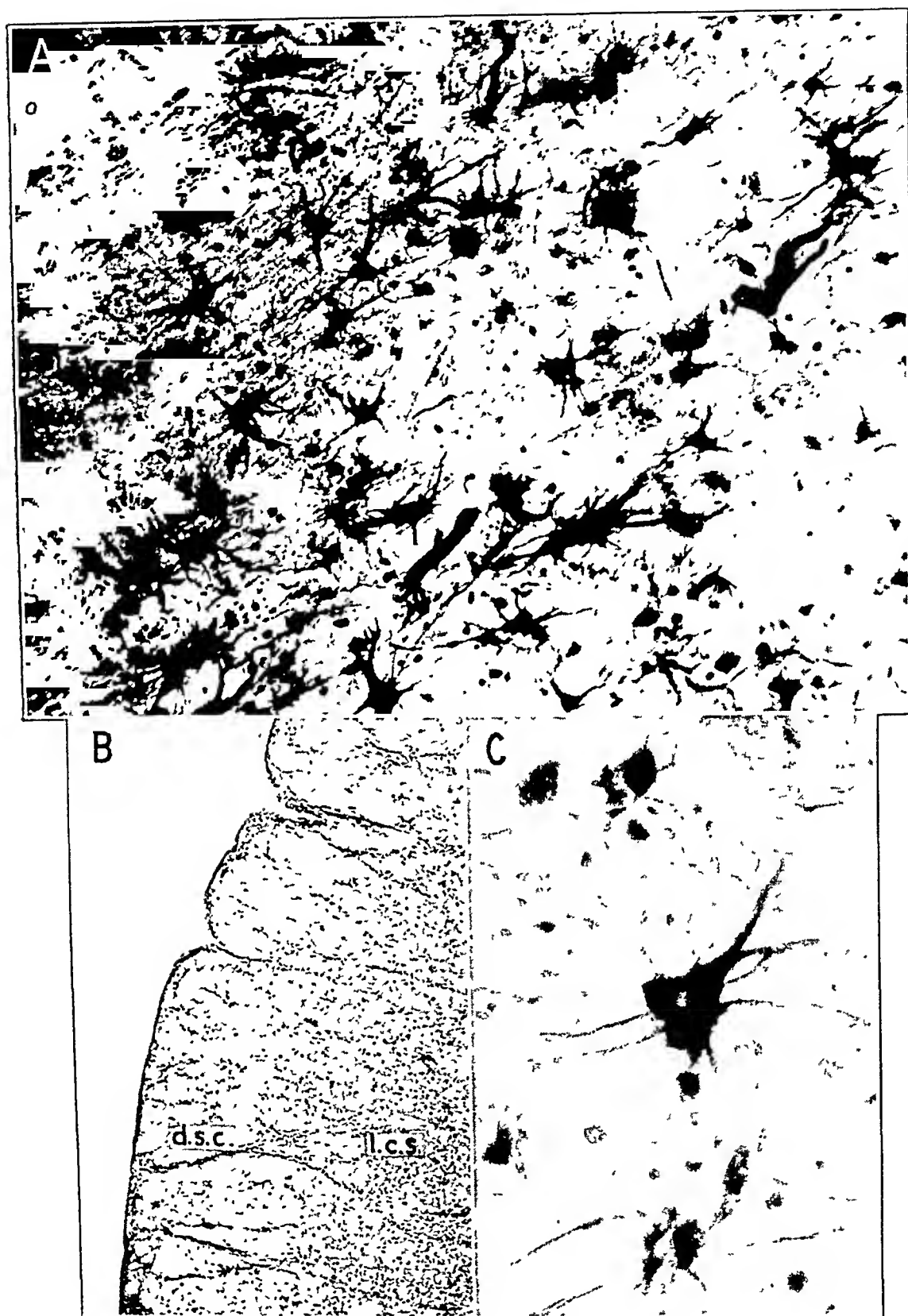


Fig. 4.—Astrocytic gliosis in the spinal cord. *A*, increase in number and size of astrocytes in the posterior horn. *B*, low power view, showing gliosis in the lateral corticospinal tract (*l. c. s.*) and absence of gliosis in the dorsal spinocerebellar tract (*d. s. c.*). *C*, monster astrocytes in the lateral corticospinal tract. Cajal gold chloride–mercury bichloride stain.

Medulla, pons and midbrain: The great majority of the ganglion cells in these structures were involved, the changes resembling those in the spinal cord. Swollen, distorted cells were seen in all nuclear groups, though the cells of the inferior olivary nucleus and the substantia nigra were somewhat less affected than most of the others. So-called mulberry bodies were seen throughout the medulla and pons. Numerous round, homogeneous cells with absence of nuclei, similar to those in the spinal cord, were observed; ghost cells and empty cell spaces were also present (fig. 2 *B*). Satellitosis was seen frequently, although neuronophagia was difficult to find. The restiform body, the brachium pontis and the brachium conjunctivum appeared normal.

Basal ganglia and diencephalon: As a whole these portions of the nervous system were the least disturbed. In the thalamus, globus pallidus and putamen only an occasional cell was involved. The cells of the caudate nucleus, however, seemed to be more disturbed. Practically all of the cells in the periventricular nuclei appeared to be normal. The internal capsule was undergoing degenerative changes; a notable increase in glial elements and the presence of considerable neutral fat in sections stained with scarlet red were noted. No mulberry bodies were observed in this entire region.

Cerebellum: All the folia of the cerebellum (fig. 5) appeared to be reduced in size. Sections from the lingula, culmen, central lobule, folium, uvula and nodule of the vermis and the quadrangular lobe, inferior semilunar lobule and tonsil of the hemisphere were similar in appearance. Disappearance of most of the Purkinje cells was striking. Only a few of these cells remained in each folium, and all of them were damaged. These remaining cells often assumed a bizarre appearance; their Nissl substance had disappeared, the cell body was either swollen or pyknotic, and their dendrites were irregularly enlarged. Neurofibrils were difficult to recognize in the cell body with the Bielschowsky stain, though they were seen in the swollen dendrites. In the absence of the Purkinje cells, the layer of glia cells (Bergmann's glia) between the granular and the molecular layer had increased in size (forming the so-called sheath of Lannois-Paviot). The basket cells and their tangential fibers and pericellular baskets were decreased in number, although those present frequently appeared normal. Pericellular baskets were occasionally seen surrounding empty spaces formerly occupied by Purkinje cells. The granule cells were moderately diminished in number, particularly in the external portion of the layer; the cells, however, appeared normal. The granular layer and the white lamina contained numerous fibrous astrocytes, many being swollen and multinucleated. While the cells of the dentate nucleus seemed to be normal in number, some were involved in the degenerative process.

Cerebral cortex: In general, alterations in cortical structure were not as marked as those in the spinal cord, brain stem and cerebellum. The most severe changes were in the motor area. The general architecture of the cellular laminae was always recognizable. The molecular layer appeared to be more dense than normal. The layer of small pyramidal cells (lamina granularis externa) seemed intact. In the motor area the layer of medium-sized pyramidal cells (III) was poorly developed, and a patchy disappearance of ganglion cells was noted. This was also true of the deeper layers. In the fifth layer no giant pyramidal cells could be detected. The cytoarchitecture of the temporal isocortex was affected to a lesser extent, disappearance of cells in the third layer being infrequent and the deeper layers relatively unimpaired. In the occipital lobe the layer of small pyramidal cells (II) and the layer of large pyramidal cells (IV a) were better developed than the others. Few abnormalities were noted in the cornu ammonis. However, cellular alterations of varying degrees were present in all portions of

the cortex that were examined. The normal contour of the cell was usually retained, even though some swelling was observed; only rarely were balloon-shaped or pear-shaped cells seen. The axis-cylinders were usually intact. Gliosis

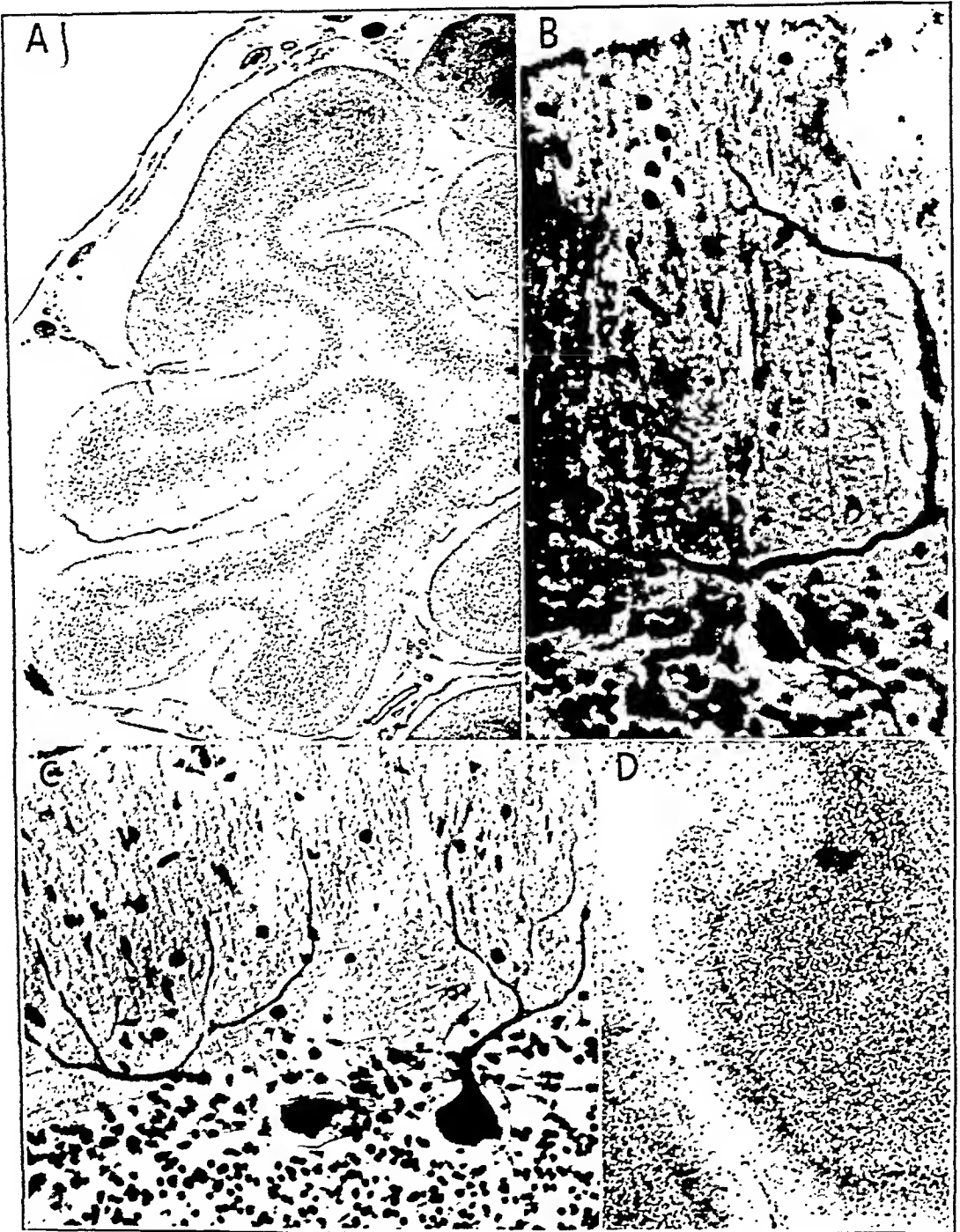


Fig. 5.—Sections of the cerebellum. *A*, low power view, showing small folia and diminution in the number of Purkinje cells (eleven of their cell bodies may be counted); cresyl violet stain. *B* and *C*, abnormal-appearing Purkinje cells, with irregular swelling of antler-like dendrites, and a pericellular basket in *C*; Bielschowsky stain. *D*, proliferation of Bergmann's glia, replacing the Purkinje cells, and rarefaction of granule cells near the molecular layer; phosphotungstic acid hematoxylin stain.

was present throughout the cortex and, to an even greater extent, the subcortical white matter. Regressive changes in the microglia and oligodendroglia were pronounced. Neuronophagia was seen more frequently in the cortex than elsewhere, leaving a residuum of partially destroyed cells and shadow forms.

Meninges: Slight cellular proliferation was noted in the pia-arachnoid, especially over the cerebellum. The cells consisted of fibroblasts, lymphocytes and wandering histiocytes. Some contained lipoidal granules; some were degenerating. A few compound granular cells were also seen.

Blood vessels: Most of the blood vessels were normal in appearance. However, in regions of marked parenchymatous change the blood vessel walls were frequently affected, especially the outer portions. In some the adventitial structures were almost completely destroyed, except for scattered connective tissue fibers and swollen fibroblasts containing lipoidal granules. The muscle cells were sometimes swollen, but the endothelium was usually normal.

Microscopic Appearance of Other Organs: Small bundles of atrophic fibers with some proliferation of the nuclei were seen in sections of voluntary muscle. The heart muscle showed pronounced signs of degeneration; atrophy, swelling and vacuolation were present. The lungs were congested and edematous. Marked swelling and degeneration of cells in the malpighian corpuscles of the spleen were observed. Numerous wandering histiocytes were present in the thymus. With the scarlet red stain neutral fat appeared in some of the Kupffer cells of the liver and the epithelial cells of the convoluted tubules of the kidney. With the Schaffer modification of the Pal-Weigert stain hematoxylinophilic granules (prelipoids) could be seen in many of the visceral organs, including the swollen cells of the malpighian corpuscles of the spleen (fig. 6*A*), the septal cells of the lung, the Kupffer cells of the liver, the muscle fibers of the heart (fig. 6*B*) and all the cellular elements of the thymus. No "foam cells" were observed.

Alterations in structure were noted throughout the entire central nervous system. These changes were greatest in the spinal cord, brain stem and cerebellum. They were least conspicuous in the basal ganglia and diencephalon. The cells and their processes, the glia and the myelin of some ascending and descending pathways were affected.

In the spinal cord, the nuclei of the posterior horn and the nucleus dorsalis were especially disturbed. The cerebellum was reduced in size. Most of the Purkinje cells were missing, and the few that remained were damaged. Bergmann's layer of glia was augmented in size. The granule cells were rarefied, and cell-free patches were noted near the molecular layer. The deeper layers of the cerebral cortex tended to be more involved than the others. The damage was greatest in the motor area, where the layer of giant pyramidal cells appeared to be absent.

The cellular changes consisted, in part, of swelling of the cytoplasm, distortion of the normal cellular architecture, disappearance of the Nissl substance and changes in neurofibrillary structure. Pear-shaped and balloon-shaped cells were observed, but these rarely reached the size ordinarily seen in cases of amaurotic family idiocy. Some of the swollen cells contained hematoxylinophilic granules, indicating the presence of so-called prelipoids. The processes of many of the altered cells were

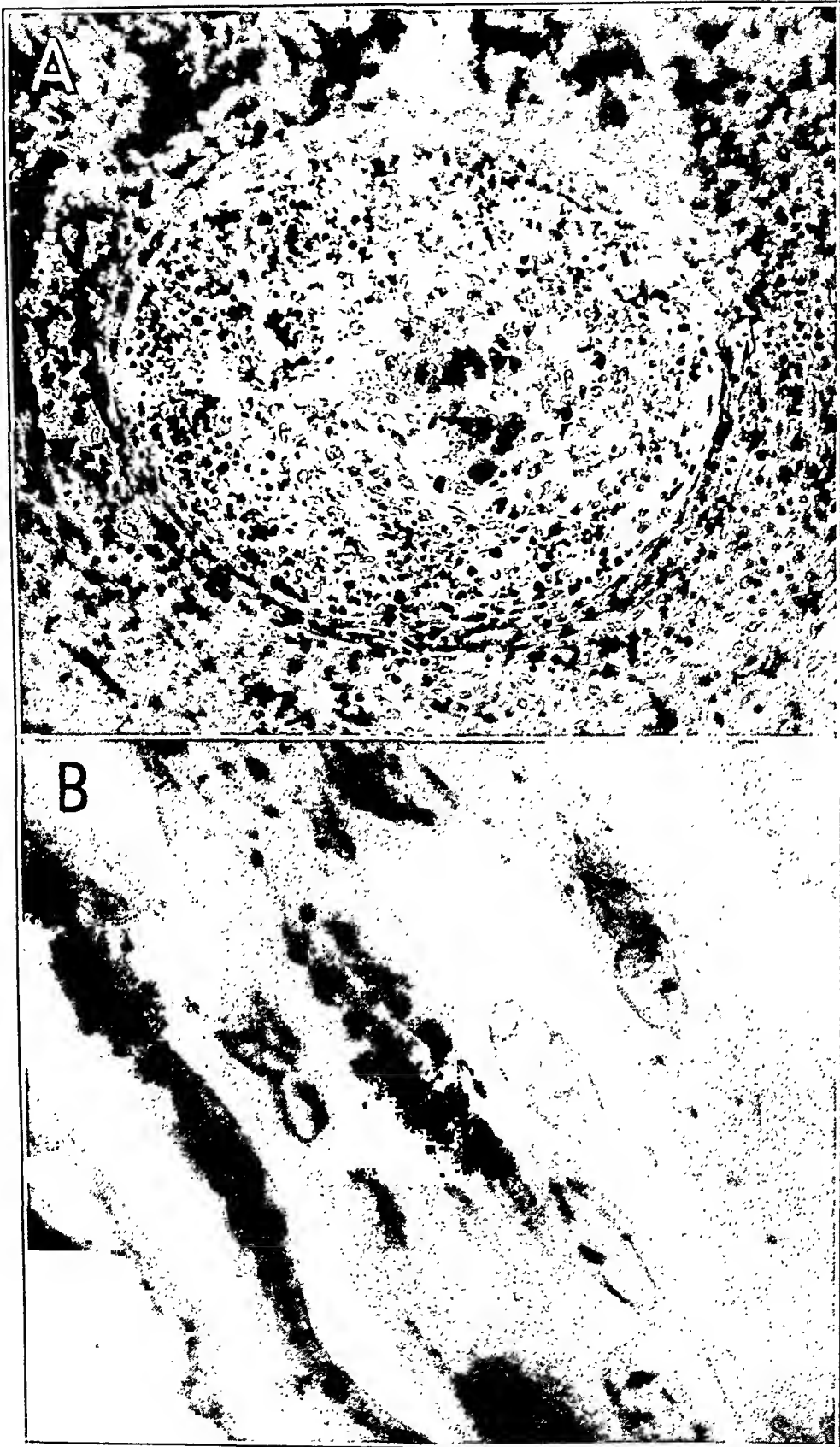


Fig. 6.—*A*, malpighian corpuscle of the spleen, with central necrosis and deposition of hematoxylinophilic granules; Schaffer stain. *B*, heart muscle fibers, showing hematoxylinophilic granules; oil immersion.

decreased or absent; remaining dendrites were sometimes of bizarre shape, with irregular expansions. Changes in the dendrites often resembled those seen in the cells. Shrunken, pyknotic cells, shadow forms and empty cell spaces were observed. The nuclei of these large cells were located at the periphery, or were even pushed into the base of the swollen dendrite.

Increase in glia was observed everywhere in the nervous system. In the basal ganglia this increase seemed to be more pronounced than the cellular alterations. All types of glia cells were involved. Numerous monster astrocytes, often multinucleated, and compound granular corpuscles were present.

Diminution in the number of myelin sheaths was observed in the lateral and ventral corticospinal tracts and in portions of the posterior column, particularly the fasciculus gracilis. The oval area of Flechsig was the only afferent pathway involved below the thoracic region. Glia cells, particularly astrocytes, were increased in these areas. Lack of involvement of the dorsal spinocerebellar tract was remarkable in view of the severe alteration in Clarke's column. In spite of serious impairment of intracerebellar connections, as evidenced by the disappearance of Purkinje cells, all the afferent and efferent cerebellar pathways were relatively intact. The conspicuous gliosis in the myelin-poor portions of the cord (fig. 3 *B*) and the presence of pericellular baskets around cell-free spaces in the cerebellum were evidence that the process was degenerative, rather than due to lack of development of these structures.

Slight cellular proliferation of the pia-arachnoid was observed. Degeneration of the walls of some of the blood vessels, most pronounced in the adventitia, may be interpreted as a secondary reaction to the parenchymatous involvement.

While degeneration of heart muscle, voluntary muscle and the malpighian corpuscles of the spleen was noted, the most striking change in the visceral organs was the appearance of numerous hematoxylinophilic granules in the spleen, liver, lung, heart and thymus.

COMMENT

The familial neurologic disorder that has been described does not readily conform to any previously described disease, either from the clinical or from the pathologic viewpoint. Certain of the changes, however, are shared by a variety of heredofamilial disorders.

Clinically the cases were marked by a flaccid type of paralysis, with retention of tendon jerks in 2 of the cases, absence of abdominal reflexes, loss of speech, difficulty in swallowing, strabismus and varying degrees of impairment of mentation. Seizures were observed in 2 of the 3 cases. Fibrillations and diminished reaction to faradic stimulation were observed

in 1 case and pale optic disks in another. The disease began during the first year of life, and death occurred about the second birthday.

In onset, fatal termination and familial occurrence the disorder was similar to both amaurotic family idiocy (Tay-Sachs disease) and infantile progressive muscular atrophy (Werdnig-Hoffmann disease). The flaccid paralysis and involvement of cranial nerves may be present in either disease. Seizures have been reported only in cases of the former. Against the diagnosis of amaurotic family idiocy are (1) absence of severe mental deterioration in 2 of the cases and (2) lack of visual disturbances. In the third case, in which histologic examination was made, the patient was able to grasp for objects until shortly before death. The absence of amaurosis is evidently exceedingly rare in cases of Tay-Sachs disease. Van Bogaert and others¹ reported the occurrence of idiocy without visual disturbances in a child of a family in which other members had the typical manifestations of the disease; no pathologic verification is available. Sachs² stated that in rare instances the visual disturbance may begin late in the course of the disease. In a few other cases reported³ the cherry red spot has not been observed.

Pathologically, the disease in this case seemed to resemble Tay-Sachs disease more than any other. Swollen, bizarre cells and dendrites were seen which appeared to be identical with the characteristic cells of this disease. Atrophy of the cerebellum and disappearance of the Purkinje cells similar to the alterations in Tay-Sachs disease were present. Involvement of pyramidal tracts, hyperplastic gliosis and "mulberry bodies" were also noted. The increase in glia in the third case was not always related to the cellular alterations—evidence that it was a primary, and not a reactive, phenomenon; this feature has been stressed by some observers in cases of amaurotic family idiocy.^{4a} In spite of these similarities, the swelling of the cells was neither as marked nor as striking as is to be expected in characteristic cases of this disorder. In addition, many cells appeared to be undergoing axonal degeneration, and empty cell beds were observed. While involvement of the cortico-spinal tracts has frequently been noted, damage to the posterior column

1. van Bogaert, L.; Sweerts, J., and Bauwens, L.: Sur l'idiotie amaurotique familiale du type Warren-Tay-Sachs. Etude sémiologique du syndrome de décérébration et des automatismes primitifs de l'enfant, *Encéphale* **27**:196-223, 1932.

2. Sachs, B.: Personal communication to the authors.

3. Epstein, J.: Amaurotic Family Idiocy Without the Classical Cherry-Red Spot, *Arch. Pediat.* **46**:124-129, 1929. Hassin, G. B., and Parmelee, A. H.: Amaurotic Family Idiocy (Tay-Sachs Type), *Am. J. Dis. Child.* **35**:87-102 (Jan.) 1928.

4. Wilson, S. A. K.: *Neurology*, Baltimore, William Wood & Company, 1940, (a) p. 884; (b) pp. 950 and 954.

is practically unique, except in the case of Frey.⁵ This author observed changes in the posterior column beginning in the lower thoracic region, affecting particularly Goll's fasciculus. This is identical with the distribution of the involvement in the present case, except for the changes in the oval area of Flechsig, which have not previously been described.

There was little histologic evidence in the third case to favor the clinical diagnosis of Werdnig-Hoffmann disease, a diagnosis that seemed likely in view of the familial character, rapid course and occurrence of flaccid paralysis with fibrillations. The pathologic changes that have been described usually consist primarily of shrinkage and disappearance of anterior horn cells, and occasionally of the motor nuclei of the medulla, pons and midbrain. Degeneration of the pyramidal tracts has been noted in a high percentage of the cases reported. Zatelli⁶ described involvement of Goll's column and of the medium-sized and giant pyramidal cells in the cerebral cortex, changes which were present in this case. It should be noted, moreover, that many of the cases reported as instances of Werdnig-Hoffmann disease have been identified only by their clinical manifestations, without benefit of histologic examination; some may have resembled our case.

In spite of the lack of close similarity to previously described heredo-familial diseases, resemblances not only to the aforementioned entities but to others may be noted. The association of combined degeneration of the pyramidal tracts and the posterior column, particularly of the fasciculus gracilis, has been observed frequently in cases of Friedreich's ataxia and peroneal muscular atrophy (Charcot-Marie-Tooth disease), less frequently in cases of hereditary spastic paralysis⁷ and only rarely in cases of amaurotic family idiocy⁸ and Werdnig-Hoffmann disease.⁹ The additional involvement of the cells of the nucleus dorsalis (Clarke's column) has been reported in association with all these disorders but the last. Similar atrophy of the cerebellum with pronounced reduction in the number of Purkinje cells has been described in cases of Marie's heredocerebellar ataxia, Friedreich's ataxia, hereditary spastic paralysis and amaurotic family idiocy. Reduction or disappearance of pyramidal cells in the motor region, particularly the giant cells and middle-sized

5. Frey, E.: Pathohistologische Untersuchung des Centralnervensystems in einem Falle von Sachs'scher familiärer amaurotische Idiotie, *Neurol. Centralbl.* **20**:836-843, 1901.

6. Zatelli, T.: Zur Klinik und Pathologie der familiären, frühinfantilen, spinalen, progressiven Muskelatrophie (Typus Werdnig-Hoffmann), *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **19**:436-450, 1912.

7. Newmark, L.: Ueber die familiäre spastische Paraplegia, *Deutsche Ztschr. f. Nervenhe.* **27**:1-23, 1904. Kahlstorf, A.: Klinischer und histopathologischer Beitrag zur hereditären spastischen Spinalparalyse, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **159**:774-780, 1937. Schaffer, K., and Miskolczy, D.: *Histopathologie des Neurons*, Leipzig, J. A. Barth, 1938, p. 50.

pyramidal cells, has been noted in cases of Friedreich's ataxia,⁸ hereditary spastic paralysis,⁷ amaurotic family idiocy and Werdnig-Hoffmann disease.⁶ Amyotrophy and damage to the anterior horn cells are seen not only in Werdnig-Hoffmann disease and peroneal muscular atrophy but in Friedreich's ataxia.^{4b}

It is obvious, therefore, that in this broad group of heredofamilial disorders certain sites in the nervous system are especially vulnerable. This, of course, is not sufficient evidence to warrant the assumption that these disease processes are basically identical. The frequent involvement of the pyramidal tracts and of a portion of the posterior column is of special interest because these pathways are the youngest, both phylogenetically and ontogenetically, in the cord, and hence probably the most susceptible.⁹

The bizarre swelling of cells and dendrites which was present in this case is often considered to be pathognomonic of amaurotic family idiocy. The swollen cells and dendrites noted by Schaffer in a case of family spastic paralysis⁷ and the pear-shaped cells seen by Teschler in a case of "chronic progressive amyotrophy"¹⁰ are examples of a similar change, however. The presence of hematoxylinophilic granules, not mentioned in these cases, may be of more diagnostic significance. They were observed not only in the cells of the central nervous system but in many of the visceral organs. Such deposits are generally described as prelipoids (such as phosphatides and cerebrosides). Similar changes in the viscera were noted in cases of amaurotic family idiocy by Kufs¹¹ (adult type) and by Davison and Jacobson¹² (infantile type), an observation favoring Bielschowsky's concept¹³ that this disease is the expression of a general disturbance in lipid metabolism.

SUMMARY

A disorder occurring in 3 siblings, leading in all of them to a fatal termination at the age of 2 years, is described. The clinical manifesta-

8. Spiller, W. G.: Friedreich's Ataxia, *J. Nerv. & Ment. Dis.* **37**:411-435, 1910. Müller, E.: Zur Pathologie der Friedreichschen Krankheit, *Deutsche Ztschr. f. Nervenhe.* **32**:137-182, 1907.

9. Brouwer, B.: The Significance of Phylogenetic and Ontogenetic Studies for the Neuropathologist, *J. Nerv. & Ment. Dis.* **51**:113-136, 1920.

10. Teschler, L.: Zur Frage der chronisch progressiven spinalen Amyotrophien (sogenannter Poliomyelitis chronica), *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **30**:229-246, 1928.

11. Kufs, H.: Sind die familiär-amaurotische Idiotie (Tay-Sachs) und die Splenohepatomegalie (Niemann-Pick) in ihrer Pathogenese identisch?, *Arch. f. Psychiat.* **91**:101-106, 1930.

12. Davison, C., and Jacobson, S. A.: Generalized Lipoidosis in a Case of Amaurotic Familial Idiocy, *Am. J. Dis. Child.* **52**:345-360 (Aug.) 1936.

13. Bielschowsky, M.: Amaurotische Idiotie und lipoidzellige Splenohepatomegalie, *J. f. Psychol. u. Neurol.* **36**:103-123, 1928.

tions consisted of (1) progressive flaccid paralysis in which the distal portion of the extremities was least involved and the tendon jerks were not necessarily absent; (2) signs of involvement of the brain stem consisting of strabismus, loss of articulation and difficulty in swallowing, and (3) varying degrees of impairment of mentation. Amaurosis was not present. The clinical diagnosis of Werdnig-Hoffmann disease was made in 1 case. In this case diffuse changes were noted post mortem. They were most severe in the spinal cord, brain stem and cerebellum. Swelling and disappearance of cells and dendrites were seen. Pathologic changes in the glia were pronounced. The pyramidal tracts and portions of the posterior column were partially demyelinated. Hematoxylinophilic granules (prelipoid deposits) were observed in both the central nervous system and the visceral organs.

The disease appears to be most closely related to amaurotic family idiocy, in spite of certain clinical and pathologic differences.

Similarities between this and other forms of heredofamilial neurologic disorder are pointed out, including the frequent involvement of the phylogenetically younger ascending and descending pathways.

Stanford University Hospitals, San Francisco.

Neurological Institute of New York.

EXPERIMENTAL NEUROSES AND PSYCHOTHERAPY

JULES H. MASSERMAN, M.D.

Assistant Professor of Psychiatry, the University of Chicago, and Research
Associate, the Otho S. A. Sprague Institute

CHICAGO

Clinical psychotherapeutic methods, once mystic, then largely empiric, have only recently begun to acquire a demonstrable psychobiologic rationale. As a contribution from the field of comparative dynamic psychology, I shall attempt to show in this report that therapeutic technics developed in the study of experimental neuroses in animals conform with certain fundamental principles of behavior, which also govern the psychotherapy of human subjects.

EXPERIMENTAL OBSERVATIONS ¹

Production of Neuroses in Animals.—By means of an automatic conditioning apparatus, cats were trained to lift the lid of a box to secure food in response to one or more signals in various sensory modalities. As a control procedure, the box was then locked, or the animal was otherwise mechanically frustrated in its food taking; under these circumstances the conditioned responses to the feeding signals were rapidly extinguished, but no other behavior abnormalities developed. If, however, the food was made freely accessible after the signal, but the act of feeding itself was rendered motivationally conflictful by administering a disturbing, although harmless, blast of air across the box at the moment of food taking, the animal rapidly acquired an "experimental neurosis," characterized by manifestations of anxiety whether it was in or out of the apparatus, hyperesthetic startle reactions, consistent "phobic" responses to the feeding signals, to space constriction or to other meaningful con-

From the Department of Psychiatry, Division of Medicine, and the Otho S. A. Sprague Institute, the University of Chicago.

1. The necessary control experiments, the various characteristic behavior abnormalities constituting "the psychopathology of animal life" and the principal methods of treating experimental neuroses are recorded in a series of 16 mm. motion picture films distributed by the department of psychiatry, the University of Chicago. I have described the apparatus and technics employed in these studies in previous publications (An Automatic Apparatus for the Central Conditioning of Small Animals, *J. Comp. Psychol.* **28**:201, 1939; Is the Hypothalamus a Center of Emotion? *Psychosom. Med.* **3**:1, 1941; Psychobiologic Dynamisms in Behavior, *Psychiatry* **5**:341, 1942). A more detailed description and analysis of the experimental results for 212 animals over a period of seven years will be included in a monograph entitled "Behavior and Neuroses," to be published.

figurations previously associated with the conflict situation, stereotyped "compulsion" and "fixation" patterns of hiding or escape, "narcissistic" or regressive manifestations, such as excessive licking and preening, and even protracted avoidance of food and self starvation to the point of extreme cachexia.

Therapeutic Technics.—The "neurotic symptoms" just described persisted for months after only from one to four "emotionally traumatizing" experiences; nevertheless, the experimental neurosis could be diminished or abolished at any time by various experimental procedures, classifiable under the following five categories:

1. Diminution of Intensity of One of the Conflictful Drives: If a neurotic animal was manually, or even forcibly, fed just before being replaced in the conflict situation, its phobic, compulsive and anxiety reactions were significantly less marked than when its hunger was intense.

2. "Reassurance," "Persuasion" and "Suggestion": If the experimenter, by petting and gentle hand feeding, patiently retrained the neurotic animal to take food from the box, the phobic responses to the signals were gradually replaced by normal food seeking; other neurotic reactions abated, and the animal eventually became capable of withstanding even the previously phobogenic air blasts without flinching. In fact, in some animals the air blasts themselves later became positive conditional signals for feeding.

3. Environmental Press: In contrast to these therapeutic methods, the feeding inhibitions could also be disrupted through environmental manipulations, e. g., by employing a movable barrier in the cage to force the neurotic animal, at the height of its hunger, ever closer to the open food box as it became filled with delectable pellets of salmon seasoned with catnip. As the animal was thus slowly but inexorably brought nearer the locus and psychologic nidus of its conflict, its anxiety and attempts to escape at first increased in intensity; finally, however, the maximally reenforced hunger drive explosively broke through the counterpoised inhibitions, and furtive, hurried gulping of food occurred. Once the motivational impasse was broken, the feeding behavior soon became more natural; normal responses to the signals returned; the "claustrophobic" reaction to the space constriction disappeared, and the other neurotic manifestations rapidly diminished in intensity.

4. "Social Example": When a cat with active feeding responses to the signals was placed in the experimental situation with the self-starved, cringing, neurotic animal, the latter gradually began to join in the food taking, although for days thereafter this could easily be disrupted and the neurosis reactivated by exhibition of the conditional signals when

the animal was alone in the cage. This method, in fact, was the least reliable of the five with regard to the permanent dissipation of aberrant manifestations in the neurotic animal.

5. "Working Through": Finally, several animals were themselves trained to manipulate a switch which controlled both the feeding signals and the automatic deposition of food in the box. If the switch was then turned off so that the signals did not operate, the animals made no attempt to feed, but continued to depress the switch until the signals again appeared before taking food. When the animals were made neurotic by the air blast technic, they at first ignored or avoided the switch; however, most animals gradually reexplored its use with increasing confidence until they had reestablished their self-signaling and feeding patterns despite repetitions of the air blast and had thus, by trial and success activity, resolved their motivational conflict and its derived neurotic manifestations. These neurotic animals, then, "worked through" their conflict in a manner denied to others not given such manipulative control of the experimental situation.

COMMENT ¹

I have elsewhere proposed four fundamental principles of behavior, which may be briefly restated here as follows:

1. Behavior is motivated by the biologic needs of the organism.
2. Behavior is contingent on, and adaptive to, the meanings of the "objective" and "social" environment as interpreted by the individual organism.
3. Behavior relieves bodily tensions not only by direct but also by substitutive or symbolic activity.
4. When psychobiologic motivations or environmental meanings become excessively confused or conflictful, behavior likewise becomes abnormally substitutive, symbolic and biologically inefficient, that is, "neurotic" or "psychotic" in character.

These propositions are confirmed by the experimental results with animals here reported. Moreover, that similar principles underlie the infinitely more complex phenomena of clinical psychiatry and are consistent with various psychotherapeutic technics may be indicated by a brief review.

The Concept of Motivational Conflict.—This concept is explicit or implicit in almost all dynamic theories of the etiology of the neuroses. Psychoanalysis has shown that in men, as well as in animals, environmentally conditioned motivational conflicts engender anxiety, which then finds both deviated expression and partial mitigation in symbolic or substitutive behavior patterns, such as phobias, compulsions, fixations

and regressions. Similarly, clinical psychotherapeutic methods correspond in rationale with those employed experimentally as follows:

Diminution of Conflictful Bodily Needs: It is generally recognized that admission to a sanatorium, bodily rest, physical therapy, temporary isolation, proper feeding, etc., are psychotherapeutically effective largely because they conform to certain of the patient's conscious or unconscious psychobiologic needs, such as those for passivity, security or just environmental relief from excessive emotional stresses. When these needs are not symbolically gratified, or the meanings of the therapeutic efforts are psychotically misinterpreted, the procedures employed are generally of little therapeutic avail. Moreover, it is probable that many sedative and hypnotic drugs relieve anxiety not so much by specific pharmacologic action as by numbing the apperception of internal emotional tensions and conflicts. Similarly, occupational therapy and bodily exercise may serve mainly as acceptable outlets for conflictful drives and thus indirectly diminish the intensity of the latter. Conversely, in psychoanalytic technic direct sexual gratification may for a time be purposely forbidden in order that related anxieties and conflicts may become pressing and thereby more accessible to analysis.

Reassurance, Suggestion and Persuasion: In these "transference" technics, the therapist, like the experimenter trusted by the neurotic animal, utilizes the dependent confidence invested in him by his subject to increase the security of the latter and thus induce him to attempt solutions of emotionally conflictful life situations previously reacted to only with paralyzing anxiety or with aberrant behavioral defenses. Thus, the psychiatrist, by the use of emotionally cathectic (and thereby thaumaturgic) verbal or other manipulative symbols, may "persuade" a neurotically anorexic, vomiting patient with intensely conflictful oral needs to take food, and may even reenforce this therapy by symbolically manipulative methods, such as having a matronly nurse do the introductory spoon feeding. Unfortunately, while such therapeutic procedures may provide highly desirable symptomatic relief, they do not resolve the manifold, deeply ingrained and stoutly defended conflicts that unconsciously actuate most human neuroses. In such cases, of course, the results of short term psychotherapeutic procedures are usually neither as striking nor as lasting as those obtained in relatively stable animals made experimentally "neurotic" by a single motivational impasse produced only a comparatively short time before corrective procedures are instituted. The psychobiologic principles involved in both cases, however, may well be nearly identical.

Forced Solution: It will be recalled that with this method the animal's feeding inhibitions were overcome by forcing it mechanically into the vicinity of attractive food at the height of its hunger; once feeding occurred, the animal's anxiety and the ancillary behavioral

aberrations rapidly diminished. Empirically, it has long been recognized that direct manipulative methods may be used successfully with normally well integrated subjects within a reasonably short time after an acutely disturbing emotional trauma. For example, experience in war psychiatry has shown that an airplane pilot who, although uninjured, exhibits excessive anxiety after a crash can frequently be kept from development of a chronic and disabling neurosis by being forced, either physically or by effective press of custom and authority, to fly another plane immediately. Similarly, acute anxiety states in soldiers are often best treated in front line stations by authoritative methods of reassurance and persuasion, followed by direct return to duty as soon as possible. In the therapy of the more chronic civilian neuroses less intensive pressures must of necessity be used, if only to preserve the patient's tenuous cooperation and rapport; nevertheless, environmental manipulations and familial, economic and other reality influences can often be brought to bear not only to diminish the secondary and regressive gains of the neuroses, but to induce the patient to face his emotional problems more directly.

"Social Example" and Identification: The principle that one emulates, and thereby "identifies," with persons whose characteristics and advantages one cherishes or envies is implicit in most pedagogy and social training and is widely applicable in psychotherapy. A person raised as a devout Mohammedan who migrates to an Occidental culture, with which he then wishes to conform, will gradually lose the intensely phobic distaste for pork more appropriate to his earlier experience. Again, a rejected, withdrawn, aggressive child, placed among secure, friendly foster siblings will tend, other factors being equal, to adopt their socially more desirable characteristics in order to share their reward of parental love and security. Similarly, states of acute disabling panic in civilians subjected to bombing or other wartime dangers are often effectively controlled by giving the person so affected a specific part in a smoothly functioning team of friends and neighbors who are engaged in some purposeful defensive or offensive activity. In simpler paradigm, the starving but anxiety-ridden neurotic cat tentatively copies and eventually readopts the environmental adaptations of a cage mate which by its normal feeding responses demonstrates that such behavior is possible and biologically successful.

"Working Through": Neurotic cats given the means (electric switch) with which to test the symbolic and reality aspects of their environment (signals and feeding) gradually "work through" and eventually eliminate their neurotically inefficient patterns in a manner impossible for cats not given access to such environmental manipulations. The achievement of progressively more efficient reality relationships through exploratory selection and channeling of adaptive activity on the

part of the subject is of great psychotherapeutic importance. Thus, even in initially subjective procedures, such as psychoanalysis, the patient must later be induced to test out and apply in actual reality manipulations the newly acquired insights into his previously unconscious object and interpersonal relationships. The deeper such analytic insights, the better will be the patient's understanding of his reality symbolisms, the more frank and accurate his evaluation of his own motivations and the more effective the working through and adjustment of his emotional problems to his daily living.

Finally, it is significant that, with allowance for individual variations, a combination of all five therapeutic procedures produced the most rapid and lasting return to psychobiologically normal behavior in the neurotic animals. So, too, in human subjects effective psychotherapy often combines, first, the initial relief of excessive anxiety through the use of various procedures directed toward the diminution of motivational conflicts; second, the establishment of an effective therapeutic influence through a working identification and rapport with the psychiatrist; third, the employment of this and other interpersonal relationships to induce the patient to establish more satisfactory norms of social conduct; fourth, the use of graded amounts of reality pressure (by the physician, the patient's family, his employer and others) to force the patient to solve his emotional problems as his diminishing anxiety permits, and, finally, the provision of vocational, recreational and other operational means that make it possible for the patient to work through his reality and interpersonal maladjustments in behavior increasingly adapted to his milieu.

SUMMARY

Artificially induced motivational conflicts in animals induce "experimental neuroses," characterized by anxiety reactions, persistent inhibitions, sensory hyperesthesias, phobias, compulsions and other aberrant behavior patterns that correspond to those in human psychopathology. These neurotic manifestations are diminished or abolished by various therapeutic technics which (1) mitigate the intensity of the motivational conflict, (2) decrease the resultant anxiety, (3) force a solution by environmental pressure, (4) furnish a "social example" of more satisfactory behavior or (5) provide the animal with manipulative means to "work through" the emotionally conflictful reality situation. These observations are consistent with certain psychobiologic principles applicable alike to comparative dynamic psychology, to semeiotic psychiatry and to clinical psychotherapeutic technics.

CONSTITUTIONAL DIFFERENCES BETWEEN DETERIORATED AND NONDETERIORATED PATIENTS WITH EPILEPSY

V. CAPILLARIES OF THE FINGER NAIL FOLD

HARRY A. PASKIND, M.D.†

AND

MEYER BROWN, M.D.

CHICAGO

Because their material was studied in institutions for the insane, the majority of writers on epilepsy have expressed the opinion that this disorder inevitably leads to mental deterioration. This view was challenged by one of us (H. A. P.)¹ in 1932, in a study made on epileptic patients seen in private, extramural practice. In that study attention was directed to the fact that only 6.5 per cent of 304 such epileptic patients presented mental changes characteristic of epileptic deterioration after a suitable lapse of time. The remaining patients in this series retained normal mental health and suffered no impairment in their ability to work at their various vocations. We have become convinced that the disorder known as "idiopathic epilepsy" is of two types: In one variety mental deterioration occurs, and in the other it does not.

In addition to the mental status, certain differences between the mentally deteriorated and the nondeteriorated epileptic patients have been studied by us. In one communication² it was shown that the hereditary background of the deteriorated patient is more heavily loaded with neuro-pathic disturbances than that of the nondeteriorated patient. The onset of the seizures was found³ to occur earlier in life among the deteriorated epileptic patients than among the nondeteriorated ones, and the deterio-

† Dr. Paskind died on March 24, 1942.

From the Department of Nervous and Mental Diseases of Northwestern University Medical School.

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3. Paskind, H. A., and Brown, M.: Age of Onset of Epilepsy: Differences Between Deteriorated and Non-Deteriorated Patients, *Am. J. Psychiat.* **96**: 59 (July) 1939.

rated patients were shown ⁴ to have a greater number of seizures than the nondeteriorated ones.

For several years we have been studying differences of a constitutional, or inborn, nature between these two groups of patients. A greater profusion of anatomic anomalies (stigmas of degeneracy) was demonstrated ⁵ among the deteriorated than among the nondeteriorated epileptic patients. In other studies we reported significant differences in the body habitus,⁶ the dactylographic patterns (finger prints)⁷ and the character of the handwriting.⁸ These studies suggest that deteriorated and nondeteriorated epileptic patients differ from each other before birth, since the differences described are inborn, or genotypic, in character.

The present communication is concerned with another constitutional mark, the capillaries of the finger nail fold.

Since 1911, when Lombard ⁹ first visualized the capillaries in the fold of skin at the base of the finger nail in the living patient, there have been numerous studies on the morphology and development of these capillaries. The majority of authors dealing with capillaries of the nail fold have come to the conclusion that their formation, which occurs during the first few years of life, is controlled by constitutional factors and that thereafter the morphologic character of the capillaries remains unaltered except for the changes induced by growth and local trauma. This was the opinion expressed by Crawford,¹⁰ Hagen,¹¹ Jaensch,¹² von

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11. Hagen, W.: Periodische konstitutionelle und pathologische Schwankungen im Verhalten der Blutcapillaren, *Virchows Arch. f. path. Anat.* **234**:504, 1922.

Lederer,¹³ Stefko,¹⁴ Ubenauf¹⁵ and Leader.¹⁶ Delbruck,¹⁷ Gänsslen¹⁸ and Fischer,¹⁹ however, expressed disagreement with this view. Strong proof of the overwhelming importance of constitutional factors in determining the morphologic pattern of the capillary loops is offered by the studies of Doxiades and Uhse,²⁰ Lehmann and Hartlieb,²¹ Mayer-List and Hubner²² and Schiller.²³ These authors have shown that the capillaries of the nail fold of identical twins bear a much closer resemblance to each other than those of nonidentical twins.

From the work of the authors cited we believe it safe to accept the morphology of the capillaries in the nail fold as a constitutional mark. We have, therefore, compared the capillaries of the nail fold of deteriorated epileptic patients with those of nondeteriorated persons similarly afflicted in order to determine whether differences here might indicate differences in constitution.

The capillaries of the nail fold were investigated in epileptic patients by Euzière, Lafon and Tøye,²⁴ Kreyenberg,²⁵ Brahm,²⁶ Mari,²⁷

13. von Lederer, E.: Die Bedeutungen Capillarmikroskopie in der Prognose und Therapie der Oligophrenie, *Monatschr. f. Kinderh.* **58**:429, 1933.

14. Stefko, W.: Die Entwicklung der Hautkapillaren in Kindesalter, *Kinderärztl. Praxis* **2**:468, 1931.

15. Ubenauf, K.: Die konstitutionspathologische Bedeutung der Capillarhemmung, *Arch. f. Psychiat.* **100**:700, 1933.

16. Leader, S. D.: Capillary Microscopy in Children, *Am. J. Dis. Child.* **44**:403 (Aug.) 1932.

17. Delbruck, H.: Archcapillaren und Schwachsinn, *Arch. f. Psychiat.* **81**:606, 1927.

18. Gänsslen, M.: Der Einfluss veränderter Nahrung auf den periphersten Gefäßabschnitt, *Klin. Wchnschr.* **6**:786, 1927.

19. Fischer, L.: Der allgemeine und örtliche Veränderungen am Capillarsystem, *Klin. Wchnschr.* **2**:1337, 1931.

20. Doxiades, L., and Uhse, W.: Neue klinische Befunde am Zwillingen, *Monatschr. f. Kinderh.* **62**:196, 1935.

21. Lehmann, W., and Hartlieb, J.: Capillaren bei Zwillingen, *Ztschr. f. menschl. Vererbungs- u. Konstitutionslehre* **21**:271, 1937.

22. Mayer-List, R., and Hubner, F.: Die Capillarmikroskopie in ihrer Bedeutung zur Zwillingsforschung, ein Beitrag zur idiotypischen Bedingtheit des vegetativen Gefäßsyndrome, *München. med. Wchnschr.* **72**:2185, 1925.

23. Schiller, M.: Zwillingsproblem dargestellt auf Grund von Untersuchungen an Stuttgärten Zwillingen, *Ztschr. f. menschl. Vererbungs- u. Konstitutionslehre* **20**:284, 1937.

24. Euzière, J.; Lafon, R., and Tøye, F. P.: Tares mentales et morphologie des vaisseaux capillaires cutanés, *Arch. Soc. de sc. méd. et biol. de Montpellier* **16**:401, 1935.

25. Kreyenberg, G.: Capillaren und Schwachsinn, *Arch. f. Psychiat.* **88**:545, 1929.

26. Brahm, A. M.: Capillarmikroskopische Untersuchungen bei genuinen Epilepsie, *Deutsche med. Wchnschr.* **55**:183, 1929.

27. Mari, A.: La ricerca capillariscopica in psichiatria, *Riv. di pat. nerv.* **40**:588, 1932.

Milewski and Wilczowski,²⁸ Schnidtmann,²⁹ Schryver-Hertzberger³⁰ and Leader.¹⁶ Altogether, 537 patients were studied by these authors. Although their methods of describing or classifying abnormalities in capillary morphology varied considerably, they expressed the unanimous opinion that bizarre capillaries and abnormalities in the development of the capillary loops are unusually frequent among epileptic patients. From 33 to 87 per cent of the epileptic patients whom they studied were found to have abnormal capillaries. The value of these studies suffers greatly from the fact that patients with primary congenital mental deficiency, who are not truly epileptic, were often included in their observations. Furthermore, none of the epileptic patients studied by these authors were said to be without mental changes.

We studied the capillaries of the nail fold in 78 deteriorated patients with epilepsy who had been committed to the Elgin, Chicago and Dixon State Hospitals and in 100 nondeteriorated patients from the outpatient clinic of Northwestern University Medical School and Rush Medical College. Of the institutional patients, 38 were males and 40 females; 58 of the extramural patients were males and 42 females. The ages of the patients were similar in the two groups, most of the patients being from 20 to 40 years of age. In order to allow time for deterioration to occur, no patient was accepted for the group not showing deterioration unless seizures had been present for at least four years; many of these patients had had seizures for decades. In both groups we were careful to exclude persons with defective mental development; in some instances this was done with the aid of psychometric tests and in others by a study of the educational and vocational experiences of the patient. No patient was accepted who had signs of focal neurologic disorder.

The skin fold at the base of the nail on the fourth (ring) finger of the right hand was studied in all subjects. Fingers which had been traumatized were not used in the present study. Photomicrographs were made of all portions of the nail fold in every subject, the magnification used being 40 diameters. From four to eight exposures were made in each case. The morphologic pattern of the capillary loop was studied from the unretouched negatives of the photographs, not from the patient directly.

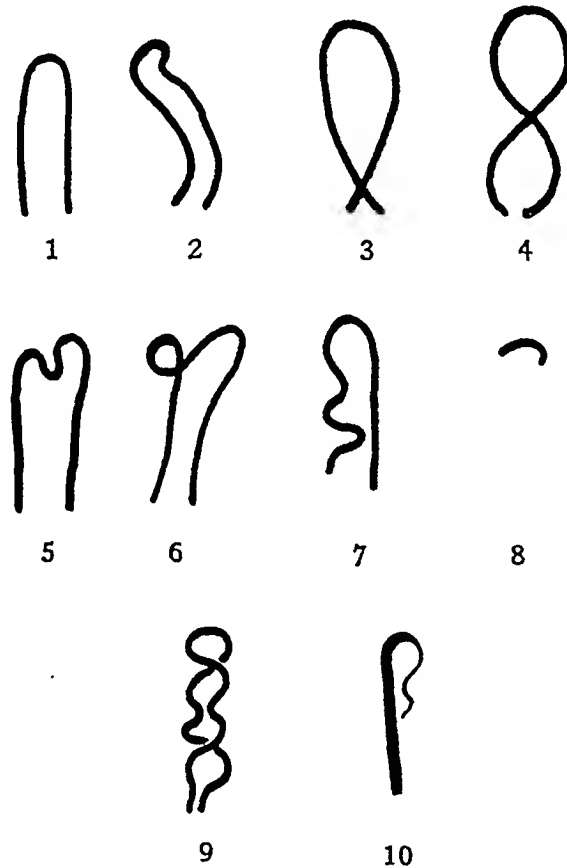
From a study of the forms of the capillary loops it is possible to classify them into ten general types. The classification is based on the morphologic pattern of the loop itself, not on its position or the character

28. Milewski, and Wilczowski, E.: Capillarskopische Untersuchungen bei Epileptikern, *Roczn. pschjatr.* **10**:79, 1929.

29. Schnidtmann, M.: Nagelfalzcapillaren und Schwachsinn, *Arch. f. Psychiat.* **94**:470, 1931.

30. Schryver-Hertzberger, S.: Ueber das Capillarbild bei Psychosen, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **141**:261, 1932.

of the blood flow within it. The figure shows the various kinds of capillary loops encountered in the patients studied. Type 1, which by many authors is regarded as the normal variety of capillary loop in the nail fold, resembles a hairpin. Both its ascending and its descending limb are well developed and straight, and they are of equal size. Type 2 resembles type 1 except that both its ascending and its descending limb are slightly tortuous, though parallel to each other. Capillaries belonging to type 3 form a simple loop, which is shaped like the written letter *l*. A figure of eight is formed by capillaries belonging to type 4. In type 5 both the ascending and the descending limb of the



Types of capillary loops encountered in the nail folds of deteriorated and of nondeteriorated patients with epilepsy.

loop are straight, but the upper portion is slightly tortuous. There is a great deal of resemblance between types 5 and 6; in the latter the upper portion of the capillary loop is more tortuous than that in type 5, and a secondary L-shaped loop is present. Type 7 represents a form in which one limb of the capillary loop is straight and the other tortuous. Under type 8 are included capillary loops which are rudimentary; they are difficult to see and appear to be partially developed. Capillary loops belonging to type 9 include those in which both the ascending and the descending limb are tortuous; capillaries which are bizarre in

appearance and do not fit into the other categories are included in this group. Under type 10 are placed all capillary loops in which one limb is much larger than the other. Only those capillary loops which were seen clearly were included in the present study.

In the table may be seen the frequency with which the various types of capillary loops were encountered in the finger nail folds of the deteriorated and of the nondeteriorated patients with epilepsy. Study of this table shows several interesting and statistically significant differences between the two groups of subjects. The simple hairpin variety of capillary loop (type 1) occurs almost three times as frequently in the nail folds of the extramural subjects as in the nail folds of the

Frequency of Occurrence of Various Types of Capillary Loops in the Nail Folds of Deteriorated and Nondeteriorated Patients with Epilepsy

	Deteriorated Patients			Nondeteriorated Patients		
	Male	Female	Male and Female	Male	Female	Male and Female
Number of capillaries observed.....	1,272	1,632	2,904	1,273	1,638	2,911
Number of patients studied.....	38	40	78	58	42	100
Types of capillary loops, percentage						
1.....	25.6 \pm 0.82	18.3 \pm 0.64	21.5 \pm 0.51	57.3 \pm 0.77	63.5 \pm 0.80	60.1 \pm 0.56
2.....	2.6 \pm 0.30	3.4 \pm 0.30	3.1 \pm 0.22	2.1 \pm 0.22	3.7 \pm 0.31	2.8 \pm 0.19
3.....	13.2 \pm 0.69	13.4 \pm 0.57	13.3 \pm 0.42	15.2 \pm 0.56	12.7 \pm 0.55	14.0 \pm 0.39
4.....	10.8 \pm 0.62	8.5 \pm 0.46	9.5 \pm 0.37	11.1 \pm 0.49	7.1 \pm 0.43	9.3 \pm 0.33
5.....	7.6 \pm 0.52	5.0 \pm 0.36	6.1 \pm 0.30	1.9 \pm 0.21	0.7 \pm 0.14	1.4 \pm 0.13
6.....	3.4 \pm 0.34	1.5 \pm 0.20	2.3 \pm 0.19	1.6 \pm 0.20	1.0 \pm 0.17	1.3 \pm 0.13
7.....	2.1 \pm 0.27	1.3 \pm 0.19	1.6 \pm 0.16	0.6 \pm 0.12	1.0 \pm 0.17	0.8 \pm 0.10
8.....	0.6 \pm 0.15	1.6 \pm 0.21	1.2 \pm 0.14	0.6 \pm 0.12	1.2 \pm 0.18	0.9 \pm 0.11
9.....	26.9 \pm 0.84	38.8 \pm 0.81	33.6 \pm 0.59	7.3 \pm 0.40	6.6 \pm 0.41	7.0 \pm 0.29
10.....	7.2 \pm 0.49	8.2 \pm 0.46	7.8 \pm 0.34	2.3 \pm 0.23	2.5 \pm 0.26	2.4 \pm 0.17

deteriorated patients. Thus, of 2,911 capillary loops visualized in the nondeteriorated patients, 60.1 per cent were of type 1; for the 2,904 capillary loops from deteriorated subjects the corresponding value was only 21.5 per cent. The same kind of difference was found when the male or the female subjects were studied separately. Types 2, 3, 4 and 6 occurred with almost equal frequency in the two groups of subjects. Capillaries classified as type 5 were significantly more frequent among female institutional epileptic patients than among female extramural patients. The same was true for capillaries of type 7. Capillary loops belonging to types 8, 9 and 10 occurred more frequently in the deteriorated subjects than in the nondeteriorated ones. This difference was also significant statistically, and it was found to remain so when the men and women of the two groups are compared with each other separately.

From the foregoing study of the morphology of the capillaries of the nail fold of 78 deteriorated epileptic patients and 100 epileptic patients without deterioration it may be concluded that the following significant differences between the two groups exist:

1. The so-called normal, or simple hairpin-shaped, capillary loop occurs more frequently in the nail folds of nondeteriorated subjects than in those of the mentally deteriorated ones.

2. Rudimentary or poorly developed capillary loops are found in a larger proportion of institutional patients than of nondeteriorated ones.

3. Tortuous and bizarre capillaries are significantly more frequent among deteriorated subjects than among nondeteriorated ones.

4. In the mentally deteriorated epileptic patients the incidence of capillary loops in which one limb is much more fully developed than the other is greater than in the mentally normal epileptic patients.

From these observations it is concluded that further evidence has been adduced to support the view that there are constitutional, or inborn, differences between the deteriorated and the nondeteriorated patient with epilepsy.

INTRACRANIAL DERMOID AND EPIDERMOID TUMORS

MAJOR JOHN MARTIN

AND

LIEUTENANT COLONEL LOYAL DAVIS *

MEDICAL CORPS, ARMY OF THE UNITED STATES

In a recent survey of the reported cases of intracranial dermoid tumors, Broager¹ stated that 62 verified cases are on record and that, of these, operation was performed in only 19. At the same time he reported that the larger series of dermoid and epidermoid tumors indicate that the latter are approximately four times as common as the former. In view of these facts, it seems important to put on record 4 cases of intracranial dermoid tumors and 1 case of epidermoid tumor (an exact reversal of Broager's ratio), in all of which operation was successfully performed, selected from a total of well over 700 verified cases of intracranial tumors.

It is not the purpose of this paper to review the statistics on all reported cases of intracranial dermoid and epidermoid tumors or to deal widely with the histology, clinical symptoms and surgical problems of such tumors. These matters have been considered in detail by Bostroem,² Brock and Klenke,³ Sweet⁴ and Broager.¹ It is of considerable interest to discover that in all of the reported series the epidermoids far outnumber the dermoids. In Cushing's⁵ total series of 2,023 verified intracranial tumors, reported on in 1932, there were 12 epidermoids and 3 dermoids. Broager's series of 759 verified tumors in Rigshospitalet in Copenhagen, Denmark, included 9 epidermoids and 2 dermoids. Courville and Kimball,⁶ in a series of 529 intracranial tumors verified at

* Consultant in neurologic surgery for the overseas forces.

From the Division of Surgery, Northwestern University Medical School, Chicago.

1. Broager, B.: *Acta chir. Scandinav.* 85:51, 1941.

2. Bostroem, M.: *Zentralbl. f. allg. Path. u. path. Anat.* 8:1, 1897.

3. Brock, S., and Klenke, D. A.: *Bull. Neurol. Inst. New York* 1:328, 1931.

4. Sweet, W. H.: *Dis. Nerv. System* 1:228, 1940.

5. Cushing, H.: *Intracranial Tumors*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

6. Courville, C. B., and Kimball, T. S.: *Bull. Los Angeles Neurol. Soc.* 1:84, 1936.

autopsy, found but 1 intracranial dermoid, and "that a small one discovered incidentally in the course of a routine examination of the intracranial contents. Love and Kernohan⁷ reported 15 instances of such tumors from the files of the Mayo Clinic; of these tumors, 10 were epidermoids and 5 dermoids (3 intracranial and intradural, 1 extracranial and 1 intraspinal). In a discussion on that paper, Sachs stated that at that time he had had 6 epidermoids and no dermoids, and Spurling reported that he had had 2 epidermoids and no dermoids. Other equally interesting reports confirm the fact that, granted that all histologic diagnoses were correct, epidermoids usually far outnumber dermoids in their frequency of occurrence in authenticated series of intracranial tumors.

Clarification is needed in the definition of epidermoid, dermoid and teratomatous tumors. Most authors agree that, with the histologic appearance of these tumors as a source of definition, the epidermoid is a benign tumor, congenital in origin, and consists only of epidermoid cells and their products of disintegration. By the same method, the dermoid is a benign tumor, congenital in origin, and may contain representative structures from a part or all of the constituents of the entire dermis. That is, a dermoid tumor may contain hair, sebaceous and sweat glands, teeth, nails and skin. Teratoma is a tumor of congenital origin; it may be either benign or malignant and contains representative tissues from all three embryonic germ layers.

The definition of an epidermoid seems simple and reliable enough. Examination of such tumors from many different clinics shows them to vary little or not at all in their microscopic structure. The capsule is a thin, friable membrane, consisting only of stratified, desquamating epithelium, such as one sees on the surface of any skin. The main mass of the tumor is composed of the products of decomposition of these epithelial cells, and while much of it is amorphous and not particularly definable, part of it is crystalline cholesterol. Crumbs of the tumor, looking much like dried bits of cottage cheese, are seen to fluoresce in ultraviolet light, and fresh smears show masses of typical cholesterol crystals, the outlines of which are made more distinct by the addition of a drop of cresyl violet stain to the fresh preparation. The term "cholesteatoma" is frequently used interchangeably with "epidermoid" in naming such a tumor. This is an undesirable and confusing practice. If "cholesteatoma" were reserved for those tumor-like masses that are actually granulomas resulting from chronic infection and that are frequently seen in various portions of the upper respiratory tract and of

7. Love, J. G., and Kernohan, J. W.: Dermoid and Epidermoid Tumors (Cholesteatomas) of Central Nervous System, *J. A. M. A.* **107**:1876 (Dec. 5) 1936.

the temporal bone, it would prevent confusion with the diagnosis of true epidermoid tumor.

For all practical as well as theoretic purposes, it would be best to reserve the term "dermoid" for those tumors which show tissues arising only from the ectoderm, such as epidermis, hair, nails, teeth and sebaceous and sweat glands. As a matter of fact, in most reports these tissues form the contents of the tumor called dermoid. In addition to these strictly integumentary structures, nerve tissue has been observed in some dermoid tumors, this inclusion being permissible if one extends the definition of dermoid to include embryonic representatives of the entire ectoderm, instead merely of the dermis. But actual difficulty does arise when a tumor, mainly dermoid in appearance, contains also some muscle fibers, bits of cartilage or bone or strands of fibrous connective tissue. Here, then, is a tumor representing two embryonic germ layers, and by original definition it is neither dermoid nor teratoma. It is of such frequent occurrence to find these mesodermal elements reported as the contents of a histologically verified and supposedly "dermoid" tumor that one wonders whether, because of this frequent histologic observation, the dermoid should be renamed in some such way as to include tissues from both the ectoderm and the mesoderm. This difficulty has also been noted by Sweet, who suggested the use of the term "teratoid" for a tumor containing elements from two germ layers. By use of the classification of "teratoid tumor" the term "dermoid," time honored and firmly established, could be preserved for the tumor containing only ectodermal derivatives. Sweet suggested the term "teratoid" for any tumor containing representatives from any two of the three primary germ layers. The adoption of this term, definition and classification is desirable, for it bridges the gap between the true, or simple, dermoid of purely ectodermal origin and the more complex tumors inclining to the teratomatous side of the scale.

The definition of teratoma is accurate and practical. Its rarity and its frequent tendency to undergo malignant change are two important characteristics.

The problem of why epidermoids and dermoids arise where they do intracranially brings out many interesting facts, theories and speculations. Courville and Kimball⁶ stated:

New growths of embryonic origin within the cranium may be divided into two groups. In the first group, the tumor arises from residual cells of some specific structure such as the craniopharyngeal canal (craniopharyngioma) or the notochord (chordoma) and is always found in the region of the parent structure. Tumors of the second group apparently arise from "cell rests" derived from the original tissue layers and are, therefore, confined to no special locality, although, to be sure, they may show a predilection for certain regions. This group is made

up of three types of tumors, all of which are relatively rare—epidermoids or cholesteatomas, dermoids and teratomas.

Bostroem² stated that early amniotic adhesions might cause a local isolation, or nest, of cells, producing an anlage for an epidermoid or dermoid, the age of the anlage determining which of these two tumors would result (up to the third week, the dermoid; fourth or fifth week, the epidermoid). Arey⁸ pointed out that dermoids, resulting from embryonic epidermal inclusions, are not infrequent along the line of fusion of various embryonic structures, such as the branchial grooves, and any place along the middorsal or the midventral body wall. Certainly, intracranial dermoids are most frequently seen in the midline, and in that position may involve the skin, the skull and the dura mater. Furthermore, the high incidence of their location below the tentorium should be explainable. Gray,⁹ citing Bland-Sutton, stated that early in embryonic life the dura mater and the skin are in actual contact. Later, the developing skull normally intervenes between the dura mater and the skin, but if such a separation is incomplete, due, for example, to a defect in bone development, then the dura and the skin may adhere to one another. Such a site of adherence may act as a tumor anlage. Also when the dura mater invaginates to form the tentorium cerebelli, a fold of skin may be caught in the dural folds, again inviting the development of a local tumor. Courville and Kimball expressed the belief that there must be some real reason for the high incidence of midline cerebellar dermoids and that "since meningoceles and encephaloceles may also be found in this situation, it is possible that dermoids may also have an embryonic basis in some sort of malformation, a disturbance of cellular rather than of structural arrangement." Love and Kernohan considered the possibility of trauma as a factor in the production of such tumors. Remnants of epidermal tissue could be carried into the deep layers of the scalp, or even between the inner and the outer table of the skull, such remnants being potential sites of tumor growth. Broager made some interesting observations on the pathogenesis of epidermoid and dermoid tumors. He stated the belief that the intracranial dermoid is of an earlier embryonic origin than the epidermoid and that the localization of the tumor depends entirely on the position of the tumor anlage in relation to the medullary sulcus. He stated:

If the anlage lies within the dorsal border of the sulcus, the tumour will be localized in connection with the ventricular system; if the anlage lies in a place corresponding to the border, the tumour will be localized in or near the median line, whether it be infra-tentorially or quite anteriorly round the lamina terminalis which corresponds to the anterior neuropore, the ultimate point of closure of the

8. Arey, L. B.: *Developmental Anatomy*, Philadelphia, W. B. Saunders Company, 1926.

9. Gray, R. C.: *Minnesota Med.* 39:530, 1939.

medullary tube; finally, if the anlage is lying more laterally towards the neural crest, the tumour may be localized laterally, on the base, in the cleft of Sylvius or on the convexity.

He also pointed out that unless a dermoid tumor lies subdurally or epidurally, it will usually be found to communicate in some place with either the pia or the ependyma. The epidermoid is most frequently seen in the cerebellopontile angle, where it simulates closely the acoustic neurinoma in clinical signs. The dermoid is rarely found in that location, and why that site seems reserved for the epidermoid is not explained by Broager.

Epidermoid and dermoid tumors situated intracranially are usually amenable to surgical treatment. Such tumors as those reported on by Gray, however, lying deep within the cerebrum and extending into either lateral ventricle, are beyond the scope of surgery. Frequently a dermoid may become infected, with resulting terminal meningitis. Or it may rupture spontaneously and spread its contents throughout the cerebrospinal fluid system, a dangerous complication but not necessarily a fatal one. Such a rupture produces a severe leptomenigeal reaction, and this, together with the actual mechanical barrier formed by the lipoid material and cellular masses, may cause blocking of the cerebrospinal fluid circulation and resultant sudden hydrocephalus. The dermoid frequently ruptures during surgical removal, for the capsule is not necessarily composed of thickened, skinlike tissue. In fact, most of the wall may be, and usually is, essentially epidermal, exactly like that of the epidermoid. The contents of a dermoid are usually lumpy masses and viscid fluid; hair may be absent or may be present in amounts from a few fine strands to matted masses. All this material is easily recoverable even though the tumor breaks up during removal. Removal of the epidermoid piecemeal is usually necessitated by rupture of the filmy, delicate capsule. Bailey, Buchanan and Bucy¹⁰ pointed out that though the tumor is easily removed because of its complete avascularity, it tends to recur, since during the surgical extirpation a few fragments of the friable mass almost invariably escape and any such particle is another tumor anlage wherever it may settle.

Because of the comparative rarity of intracranial epidermoid and dermoid tumors, and because of the stimulation which consideration of their pathogenesis brings about, the histories of the following 5 cases are given in condensed form.

REPORTS OF CASES

CASE 1.—E. K., a single woman aged 21, began to experience early morning headache one year before coming under observation. At first the headaches were

10. Bailey, P.; Buchanan, D. M., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*, Chicago, University of Chicago Press, 1939.

supraorbital and suboccipital, later becoming constant and more or less generalized. Eventually they were accompanied by vomiting without nausea, but shortly before her admission to the hospital the vomiting ceased. For the previous six months she had noticed increasing numbness of the right side of her face, and for two months, gradual failure in visual acuity. In walking she found it difficult to maintain good balance, and she inclined to stagger toward the right. There was no history of trauma to the head.

On examination she was found to have high grade bilateral papilledema and visual acuity was greatly decreased, but there was no defect in the visual fields. The right corneal reflex was absent; the right side of the face and tongue showed decided diminution of sensation to pain but not to touch, and the right side of the face and palate did not move as well as did the left. The gait was ataxic, but she could perform accurately the finger to nose and heel to knee tests. There was no nystagmus or alteration in the movements of the extraocular muscles. The deep tendon reflexes of the right upper extremity were moderately diminished as compared with those of the left, but they were equal in the lower extremities. All abdominal reflexes were present, and there were no pathologic plantar reflexes. No difficulty in speech or swallowing was noted. Lying exactly over the external occipital protuberance there was a soft, fatty nodule the size of the tip of a finger, and on its apex was a small, dark red papule. This mass was tender when palpated and had been present since birth.

Roentgenograms of the skull showed prominent convolutional impressions. The sella was fairly large, and there was extensive thinning of the posterior clinoid processes. It was typically a sella which had undergone changes as a result of intracranial pressure originating outside the structure itself. The spinal fluid, which was under moderately increased pressure, contained but 6 cells per cubic millimeter and was without other significant characteristics.

The mass over the suboccipital ridge suggested an old meningocele, but the presence of an underlying congenital tumor was not excluded. The patient underwent operation on Aug. 28, 1931. Exactly in the midline between the two cerebellar hemispheres and occupying entirely the usual site of the cisterna magna was a dark greenish blue mass overlying the vermis and extending through the foramen magnum. The mass was contained within a limiting thick, hypertrophic arachnoid membrane and could be wiped away from the surrounding structures with moist cotton sponges. The removal was accomplished from below upward, until the tumor was seen to end in a necklike extension leading from the tentorium to the soft mass in the midline of the scalp. This extension, as well as the subgaleal mass on the scalp, was filled with a cheesy green material and a mass of matted blond hair. The entire tumor was removed, and the patient made an entirely uneventful recovery.

The specimen contained much fine hair, flakes of calcified material, coarse and granular cheesy, amorphous material, masses of epithelial cells in all stages of disintegration and a large amount of thick, brown, viscid, noncellular material, which hardened to a consistency of hard rubber in a 10 per cent concentration of solution of formaldehyde U. S. P. The diagnosis was dermoid (teratoid) tumor (figs. 1 and 2).

CASE 2.—L. M., a single woman aged 32, a deaf-mute, was brought to the hospital by ambulance in a comatose state. For a year and a half she had suffered from headache, at first localized to the back of the head and upper cervical region,

but of late becoming generalized. On three occasions she had lost consciousness during the height of a severe bout of headache. For a year she had suffered increasing difficulty in walking, until at last, for one week, she had been completely unable to walk, not because of weakness but because of complete loss of balance. She had had sudden attacks of nausea and vomiting for six months, difficulty in swallowing for four months, sudden attacks of vertigo, especially on change of position, for three months and double vision for one month prior to admission to the hospital. She had lost a great deal of weight, and her disposition had become one of fear and great concern. In fact, six months before she came under observation she had been a patient in another hospital, where the diagnosis of "hysteria" was made. In spite of a feeling of swelling and numbness in her tongue, she had an enormous appetite and ate with relish. There was no history of injury to the head.

The patient was found to have an extreme degree of papilledema on both sides, the elevation being recorded as high as 6 D. There were multiple retinal hemor-

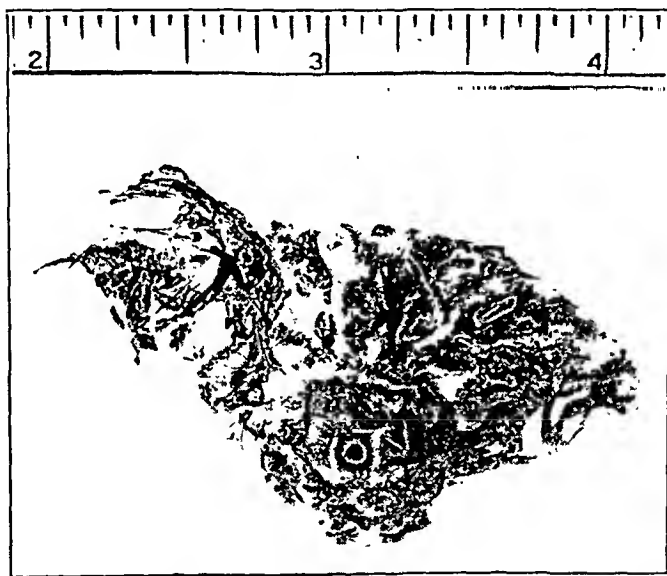


Fig. 1.—Dermoid (teratoid) tumor, total specimen. Note the masses of fine hair, the flakes of calcified material and the principal mass of amorphous tissue debris.

rhages but no defect in the visual fields. She complained of diplopia, but tests showed that all extraocular muscle movements were well performed except that convergence was poorly done. When she looked to either side there was marked nystagmus, with the quick component to the side of the gaze. Corneal and facial sensation to pain and touch was intact. There was obvious weakness of the muscles of the left side of the face, and the muscles of the pharynx and palate contracted poorly. When the patient was placed in the upright position she promptly fell backward and to the right. She was ataxic in all extremities, but testing revealed that she was more so on the left than on the right. There were no reflex changes of any nature and no pathologic reflexes, and responses to sensory tests were normal throughout.

Roentgenograms of the skull revealed nothing of significance except the presence of fairly prominent convolucional impressions.

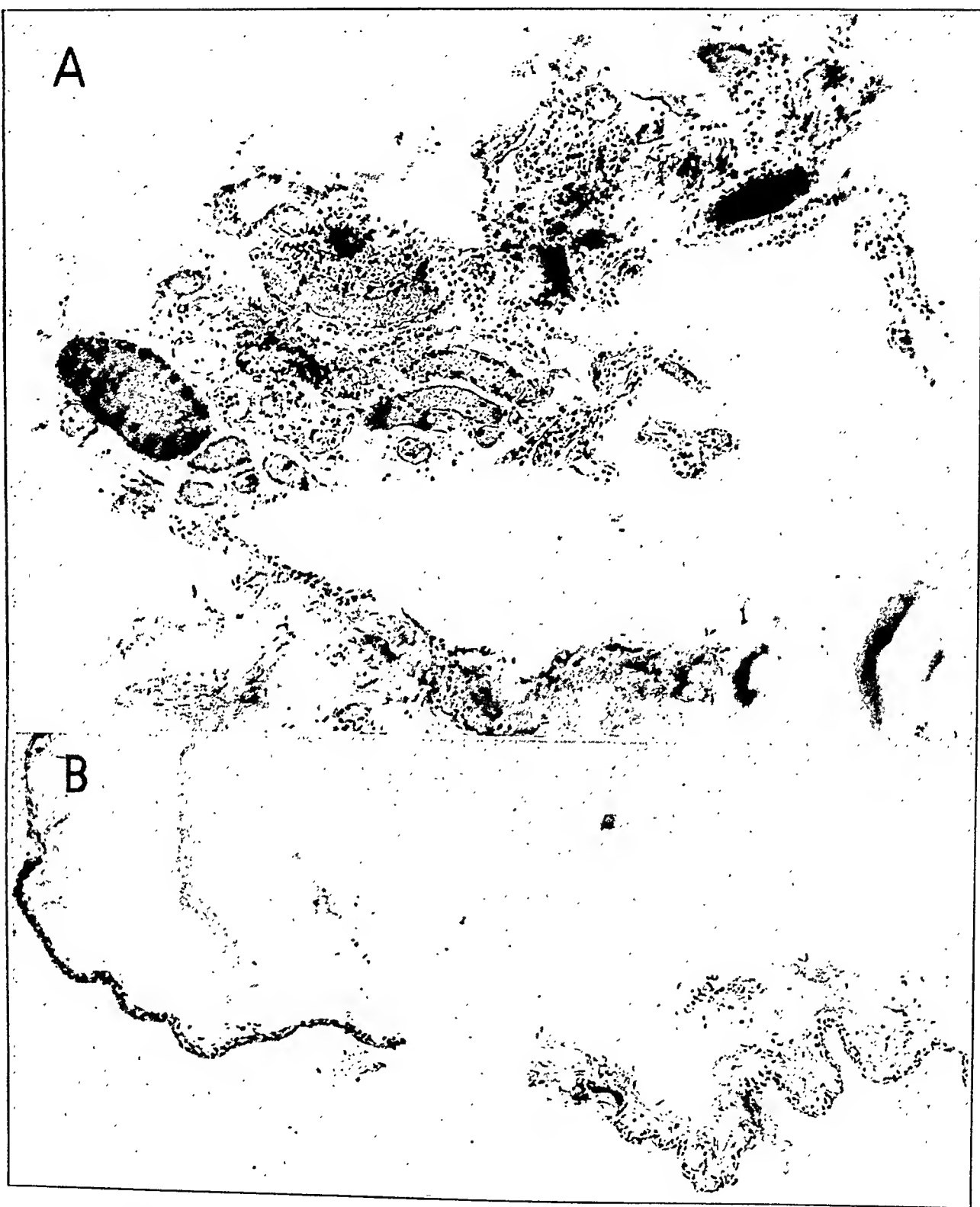


Fig. 2.—*A*, section of a dermoid tumor. Thin-walled blood vessels, coils and masses of simple epithelial cells and isolated, desquamated epithelial cells are the only stained structures. The viscid, heavy fluid which this tumor contained was free of cells and did not stain.

B, wall of a dermoid cyst. This delicate membrane is composed of epithelial cells arranged in from one to three layers. The wall of this cyst may be compared with that of an epidermoid tumor, as shown in figure 4.

Hematoxylin and eosin; $\times 75$.

A bilateral suboccipital craniectomy was performed on July 7, 1933, and a large greenish cyst was observed to overlie the left cerebellar hemisphere and extend to the midline. During separation from the cerebellar cortex the wall of the cyst broke, with freeing of a thick, brown, tenacious material, which flowed slowly. When this material was removed the bottom of the cavity was observed to contain large, yellow, granular masses, which had the gross appearance of cholesterol crystals. When this material was removed a mass of tangled hair was seen in the depths of the cavity. When, at last, all the contents were removed, the cavity was perfectly clean, and cerebrospinal fluid once more circulated in the posterior cranial fossa. The cyst did not extend into the vermis and did not touch the tentorium. The cisterna magna was pushed to the right but was intact, and the right cerebellar hemisphere was in no way invaded. No definite point of origin for the tumor could be determined. The diagnosis was dermoid cyst.

The patient was discharged from the hospital on July 23. She walked fairly well, though with some residual ataxia, and the nystagmus had disappeared, together with her headache. Two months later the papilledema had completely disappeared, and she walked without any loss of balance and considered herself well in every way.

Case 3.—O. M., a woman aged 27, single, a bookkeeper, entered the hospital complaining of persistent occipital headache, which had been present for nine months. This discomfort was invariably worse in the afternoon; it was made worse by straining or jarring, and at no time was the headache accompanied by nausea or vomiting. One month before admission she began to notice blurring of vision, and at the same time her headache was usually accompanied by flickering, dancing lights before her eyes. Three weeks before admission she suddenly became "blind" for a minute or so while at work.

The patient was cheerful, cooperative and intelligent and appeared in good physical condition except for the complaints mentioned. Examination revealed pronounced bilateral papilledema, but no defect in the fields of vision. All extra-ocular muscle movements were well performed, and there was no nystagmus or diplopia. Slight diminution of touch sensation was present over the right side of the face, and there were slight but definite signs of weakness of the muscles of expression on the left side of the face. There was no difficulty of speech or swallowing and no change in the action of the palate or the muscles of the tongue. The patient was not ataxic in any extremity, and her station and gait were entirely normal. The deep and superficial reflexes were present and equal on the two sides, and there were no pathologic reflexes. Complete and repeated testing failed to elicit any further objective signs of neurologic change.

On Sept. 19, 1938, ventriculographic examination disclosed rather pronounced internal, symmetric hydrocephalus, the third ventricle lying directly in the midline. The fourth ventricle was not visualized. The ventricular fluid contained 25 lymphocytes per cubic millimeter, and the total protein content was 16.2 mg. per hundred cubic centimeters. No significant bony changes in the skull were discovered.

On September 23 a bilateral suboccipital craniectomy was performed, and when the occipital sinus was ligated there was a sudden escape of thick, green, sticky material from under the dura mater. When the dural flaps were turned back a cyst, lying directly in the midline, was observed to extend from high between the cerebellar hemispheres, but not reaching the tentorium, to and through the foramen magnum. It was globoid above and separated the hemispheres, but below, where it separated and compressed the cerebellar tonsils, it narrowed considerably into a

tonguelike structure. The tumor was soft and friable, but it stayed fairly well contained within its thin wall and was eventually wiped completely free of all attached brain tissue. It contained much thick, greenish brown, viscid fluid; chips of a hard white substance much like bone; crumbly, yellow masses which looked like cholesterol, and many strands of fine hair. Though the brain tissue was in no place invaded, the vermis, as such, could not be identified. The histologic diagnosis was dermoid (teratoid) tumor. The gross and microscopic appearance of this tumor was much the same as that of the tumor in case 1.

The patient was discharged from the hospital two weeks after her operation, and her postoperative course was entirely uneventful. She returned to work two



Fig. 3.—Section from a solid nodule of tissue from a dermoid cyst, showing connective tissue, epithelial cells without particular arrangement, fat cells, capillaries and clefts filled with cholesterol, in an arrangement commonly seen in dermoid ("teratoid") tumors. Hematoxylin and eosin; $\times 190$.

weeks later, has since married and has had no recurrence of any of her former symptoms (fig. 3).

CASE 4.—J. V., a boy aged 2 years, was brought to the hospital because of persistent vomiting for eight months, staggering gait for two months and extreme fretfulness and loss of appetite. Prior to the onset of the vomiting he had begun to walk normally, seemed alert and intelligent but made no attempts at talking. The vomiting began with an attack of influenza and continued unabated to the

date of admission to the hospital. For two months he had lurched from side to side when walking, and if left standing alone would fall either forward or backward. For one week he had been completely unable to stand. For six months the mother had noted a rapid increase in the size of his head and had noticed also that he held the head tilted to the left. For three weeks there had been persistent internal rotation of the left eye, and it became increasingly obvious that the child could not see well. Furthermore, he stopped saying the few words that he had managed to learn and emitted only a peculiar grunting sound.

His birth had been normal; he was well developed and had never received an injury to his head.

When examined he was found to be extremely irritable and easily frightened. There was prominent frontal, parietal and occipital bulging of the head, which measured 55 cm. in its greatest circumference. He refused to lift his head from the pillow. There was a positive Macewen note when the skull was percussed. The disks were pale and greatly swollen; the retinal veins were engorged and tortuous, and many fine retinal hemorrhages were seen. The right pupil was larger than the left; both were dilated and reacted only sluggishly to light. There was no nystagmus. The left eye was not moved laterally but rested most of the time in a position of internal strabismus. There was no facial weakness and no apparent loss of sensation in the trigeminal area on either side. He used both hands and legs equally well. The right knee jerk was greater than the left; ankle clonus and a strong Babinski sign were elicited on the right side. There was no apparent loss of sensation at any point on the body. Forward flexion of the head caused him to cry out with pain.

Roentgenograms of the skull showed prominent convolutional markings and separation of the suture lines.

A diagnosis of tumor of the posterior fossa, most probably medulloblastoma, was made. However, on Feb. 24, 1941, at the time of the operation, a change in this diagnosis was made, after the head had been shaved and the scalp was being prepared. Immediately over the site of the external protuberance there was a small scar in the skin, and a low, soft, subcutaneous nodule could be felt. With slight pressure a droplet of sebaceous material escaped from the scar, and this fact, together with the information obtained in the history that from this area a "sebaceous cyst" had been removed when the child was 4 months old, led to the diagnosis of dermoid cyst. A midline suboccipital craniectomy was done, and immediately a firm, yellow, spherical mass, the size of a small English walnut, was observed lying exactly in the midline, just caudal to the external occipital protuberance. It appeared to be contained within the layers of the dura mater, with an upward extension by a cordlike process through the bone to the small area of scar on the scalp. The mass was opened with the electrocautery, and there was an immediate extrusion of thick, cheesy, white and green material, together with masses of hair and particles which looked like flakes of cartilage. The entire wall of the cavity was cleansed free of this material. It was then apparent that the mass did not extend to the subarachnoid spaces but was enclosed on all sides by true dura mater. The walls of the cavity were coagulated; the remaining dead space was eliminated by fine silk sutures, and the wound was closed without drainage. The histologic diagnosis was dermoid (teratoid) tumor. Except for the age of the patient, this history corresponds closely to that in the case reported by Quade and Craig,¹¹ especially as to the location and gross appearance of the tumor.

11. Quade, R. W., and Craig, W. M.: Proc. Staff Meet., Mayo Clin. 14:459, 1939.

The child made a good recovery from the operation; his appetite and disposition rapidly improved, and he was soon able to walk steadily when led by one hand. Nine months after operation there was still some residual weakness in the left lateral rectus muscle.

CASE 5.—S. K., a housewife aged 59, was well until eight years prior to her admission to the hospital. At that time she began to notice unsteadiness in gait, so that she was soon forced to walk with a cane. Eventually she could walk only with assistance. At the same time a loud ringing developed in the left ear, which persisted for a year, at the end of which period she became totally deaf in that ear. For one year she had had increasing clumsiness in the use of the left

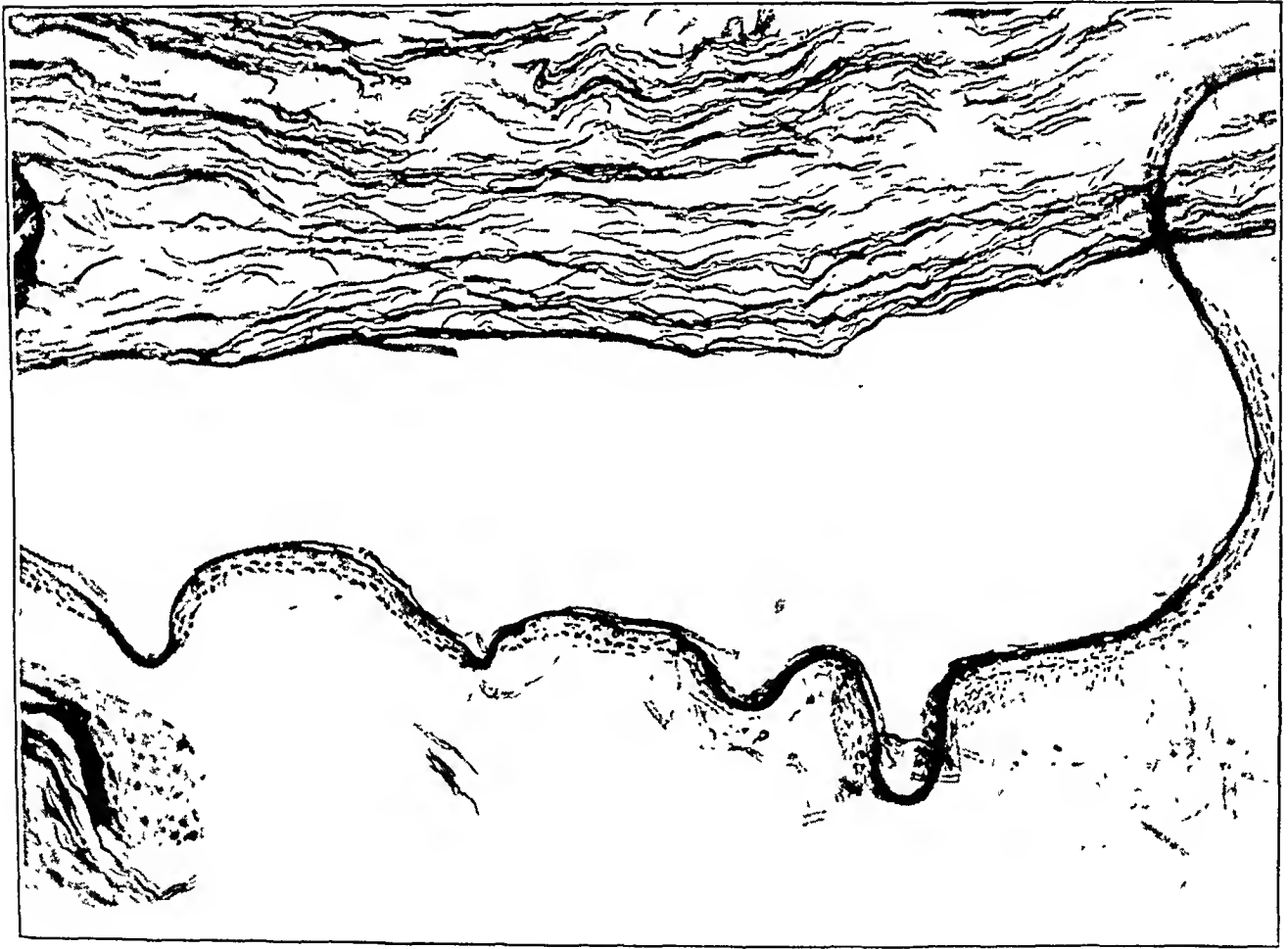


Fig. 4.—Epidermoid tumor. Note the simple arrangement of cells comprising the wall of the tumor. The process of superficial desquamation is well illustrated. The wiry, striated-appearing mass is composed of fixed cholesterol and epithelial debris. Hematoxylin and eosin; $\times 145$.

arm and hand, and for the same period she had had pronounced double vision on looking to either side, so that most of the time the left eye was held shut. For eight months she had suffered episodes of projectile vomiting, not related to meals, and her weight had decreased 40 pounds (18.1 Kg.). She had occasional headaches of a generalized nature. Of recent months there had been a tingling sensation in the left maxillary area. There was no history of trauma to the head at any time, and her past medical and surgical history was without significant incidents.

When the patient was first seen in the hospital she vomited readily on sudden change in position of the head, always fell to the left when she attempted to stand or walk and held her head with the occiput directed toward her left. The pupillary reflexes were normal, and the fields of vision were intact. The left palpebral fissure was slightly wider and the left nasolabial fold appeared shallower than the right. There was no papilledema. On looking to either side, she had



Fig. 5.—Wet smear in glycerin of material from an epidermoid. *A*, a small cluster of cholesterol crystals, together with other amorphous material. Note the typical notched corner on the crystals. $\times 225$.

B, free desquamated epithelial cells, frequently seen in such mosaic-like formation, all of their five or six sides touching other cells to form sheets, such as are shown here. $\times 300$.

coarse nystagmus, with the quick component to the side of fixation. On her looking upward, the left eye did not rotate as far as the right, and nystagmus was produced, with the movement upward and to the right. The left corneal

reflex was diminished, and though she complained of various peculiar paresthesias in the left side of the face, there was no loss of sensation to pain and light touch in that area. The caloric test failed to elicit any response whatever in the left ear. The palatal and pharyngeal muscles were unimpaired, and she swallowed without difficulty. There were pronounced dysmetria and ataxia of both the left arm and the left leg. She appeared to have practically no control over the left arm when purposeful movements were attempted, though there was no loss of muscle power. The left biceps reflex was greater than the right, but otherwise there were no variations in either the deep or the superficial reflexes, and no pathologic reflexes were present.

Roentgenograms of the skull showed no changes from the normal.

On May 26, 1941, a suboccipital craniectomy was performed, with the expectation of finding an acoustic neurinoma on the left side. The bone on the left was unusually thin for an adult, and the left cerebellar hemisphere was plainly lying higher in the operative opening than was the right. The cisterna magna was completely collapsed. The right lateral ventricle was tapped, and this reduced the intracranial pressure sufficiently to allow good retraction of the left hemisphere. Immediately there was exposed a shining, white, finely nodular tumor, the size and shape of a small hen's egg, which lay on and stretched over the surface of the seventh and eighth nerves and extended down to the eleventh nerve. The brain stem was plainly displaced to the right. The tumor appeared to have a thin, onion-skin-like capsule and was completely avascular. When the capsule was opened, the contents were easily and completely removed with a large dull curet, leaving the capsule collapsed like a thin cellophane bag. Then, with gentle traction and separation of the capsule from the surrounding structures with wet cotton pledgets, the entire capsule was removed, the procedure leaving intact the badly thinned-out eighth nerve and the somewhat attenuated seventh nerve. No bleeding followed the removal of the capsule from the side of the brain stem.

The patient made an excellent recovery, left the hospital on the sixteenth postoperative day and forty-five days after her operation was walking alone, though with residual ataxia. She had gained weight, and the diplopia had improved, though there was still some impairment in function of the left abducens nerve. The mild weakness of the left side of the face, present before operation, was somewhat increased afterward, but this, too, showed improvement one month after operation.

Particles of the tumor had a glistening, white, pearly appearance, felt oily between the finger tips and, when floated in water, produced fine oil droplets. Wet smears revealed large masses of cholesterol crystals and much other amorphous material, and stained sections showed the capsule to be made up of one or two layers of squamous or low cuboidal epithelium arranged in simple pattern. The tumor contained no other type of material of cytologic form. The diagnosis was, therefore, epidermoid tumor (figs. 4 and 5).

SUMMARY

A restatement of the definitions of epidermoid and dermoid is necessary for the proper use of these terms:

1. An epidermoid tumor is a benign neoplasm, arising from an embryonic inclusion, or nest of cells. The tumor consists of epidermal cells in various stages of disintegration, together with variable proportions of crystalline cholesterol: This tumor, containing cellular components

only from the epidermis, should not be confused with cholesteatoma, which is a product of chronic inflammation.

2. A dermoid tumor is a benign neoplasm, arising from an embryonic inclusion or nest of cells, the contents of which may represent part or all of the derivatives of the ectoderm.

3. A teratoid tumor contains representatives from the ectoderm and either one of the other two germinal layers. This tumor bridges the gap between the true dermoid and the true teratoma, which contains components of all three germinal layers.

In most large series of verified tumors epidermoids are four times as common as dermoids, but in our own group of over 700 verified intracranial tumors this proportion is reversed.

Epidermoid and dermoid tumors may become manifest at any age, and they do not show any particular relationship to sex, trauma or other incidents in the medical history.

The dermoid occurs at many different intracranial sites, but is frequently attached to the dura mater, is commonly seen in the midline and most often lies below the tentorium cerebelli. The epidermoid is practically always located in the cerebellopontile angle.

Frequently roentgenograms reveal local erosion of bone in the skull, with an area of sclerotic bone immediately surrounding the eroded area, and within the eroded space flecks of calcium may be visible. Such lesions should not be regarded as infallible evidence of the presence of an intracranial epidermoid or dermoid tumor, since other intracranial tumors may produce the same roentgenologic changes.

These tumors may be operated on successfully. In all 5 of our cases the patient has completely recovered from the operation. Two patients who were not immediately relieved of all their neurologic symptoms were greatly improved immediately after operation and are still improving.

Northwestern University Medical School, Chicago.

SIBLING DEATHS IN THE ANAMNESES OF SCHIZOPHRENIC PATIENTS

SAUL ROSENZWEIG, PH.D.

AND

DOUGLAS BRAY, M.A.

WORCESTER, MASS.

In the course of an intensive study of several schizophrenic patients the incidental observation was made that the anamnesis contained one or more sibling deaths. The experience of such deaths appeared to have a clear dynamic relationship to the psychotic mechanisms and symptoms of these particular patients. It thus seemed desirable to investigate the frequency of such frustrating situations and, even at the risk of obscuring the important individual dynamics, to approach the problem at first on a purely statistical plane. By comparing the frequency of sibling deaths in the early life history of schizophrenic patients with their occurrence in the early experience of other psychotic patients and in that of a group of normal persons the empiric fact could be evaluated. The elucidation of the results, if positive, was conceived to follow as a more or less independent qualitative study.

METHOD OF INVESTIGATION

The present initial study was limited to males to make possible the accumulation of a homogeneous group of cases sufficiently large for statistical analysis. In examining the case records and questionnaires from which the data of this study were gathered attention was centered on the occurrence of sibling deaths. Since such deaths were regarded as of possible significance in the psychosis only if they occurred during the patient's lifetime and previous to the onset of his illness, only sibling deaths which happened after the patient's birth and before the onset of the psychosis were included. Since, furthermore, the onset of the schizophrenic psychosis is often insidious and difficult to determine but is generally held to lie somewhere in adolescence, the psychosis was arbitrarily assumed for all cases in the study to have appeared by the end of the eighteenth year. Concretely, therefore, all sibling deaths which took place after the birth of the patient and before the beginning of his nineteenth year of life were counted as of possible significance. Such conditions would obviously have much less, if any, value for the control groups, but for control purposes they were necessarily invoked there too.

The data on the psychotic patients were obtained from the examination of 640 case records at the Worcester State Hospital. These records were selected

From the Research Service of the Worcester State Hospital.

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from three diagnostic groups: (1) patients with schizophrenia, in which the chief interest of the study lay; (2) patients with manic-depressive psychosis, and (3) patients with dementia paralytica. The last two served as control psychotic groups.

Rigorous criteria were established for the acceptance of case records. All records in which definite information about sibling deaths was given were included. Statements such as "two brothers died in infancy" were not acceptable since they left doubt as to whether the patient was yet born. While, in keeping with the criteria, no case record was included unless the information on sibling deaths was unambiguous, this provision was not extended to all sibling deaths mentioned. For most purposes in the present study the percentage of subjects with a sibling death rather than the characteristics of the dead siblings was of chief interest. Any case in which unequivocal data on some one dead sibling were given could therefore be included. When the death of a sibling was not mentioned, the record was retained only if the informant was mother, father, brother, sister or some other person who, to judge from the general quality and detail of the childhood information, would apparently have known of such a death had it occurred.

By these criteria only 356, or 56 per cent, of the 640 case records examined were found adequate. Table 1 shows the distribution of the records for each

TABLE 1.—*Percentage of Adequate Case Records for Each Psychotic Group*

Diagnostic Group	Number of Case Histories Examined	Number of Case Histories Accepted	Percentage Accepted
Schizophrenia.....	195	124	64
Manic-depressive psychosis.....	188	102	54
Dementia paralytica.....	257	130	51
Total.....	640	356	56

diagnostic group. While the differences in the percentages of adequate records are not statistically significant, the fact that the greatest number was obtained for the group with schizophrenia and the smallest for the group with dementia paralytica is possibly explained by the modal age of onset of the psychosis. The earlier the onset the greater the likelihood that a member of the immediate family will be still alive to provide the early history. Moreover, the schizophrenic patients in the study consisted largely of a special research group on whom data had been obtained rather carefully.

From each of the 356 adequate case records the following items of information were taken: diagnosis, age, age at onset of psychosis, total number of siblings, patient's ordinal position in the family, occurrence of sibling deaths, age of patient at time of such deaths, relative difference in age between the patient and the dead sibling, death of mother or father and age of patient at time of such death. For most of the patients additional data were gathered concerning religion, education, native country and parents' native country. The information beyond that directly concerned with death of siblings was included to serve as a context for the final analysis of the results.

Normal control data were gathered by a questionnaire covering the chief points listed in the preceding paragraph. It was sent to 250 persons comprising a group of attendants at the Worcester State Hospital, applicants at the United States Employment Office in Worcester, Mass., members of the Worcester Y. M. C. A. and classes at Clark University, American International College and

Tufts College.¹ Socioeconomically, the hospital attendants and employment office applicants were regarded as approximately matched with the psychotic patients, since they represented either a low income group (\$10 per week plus maintenance) or the unemployed. To test this matter with the other groups sampled, the Y. M. C. A. members and two of the college groups (Clark University and American International College) were asked to indicate their average monthly rentals. The median of these amounts was \$37, which is slightly higher than that found by Faris and Dunham² (page 243) for schizophrenic patients as a group but lower than the figures for patients with dementia paralytica and manic-depressive psychosis. Since it is impossible to determine how closely the patients at the Worcester State Hospital resembled socioeconomically those investigated by Faris and Dunham in Chicago, this comparison is at most indicative of only a rough matching between the normal and the psychotic subjects in the present study. For this reason special care must be exercised in the evaluation of such differences between the groups as are revealed by the data.

TABLE 2.—*Percentage of Subjects with a Sibling Death During the Subject's Childhood or Adolescence*

Group	Number of Subjects	Number with Sibling Deaths	Percentage	Standard Deviation of Percentage
Schizophrenia.....	124	49	39.5	± 0.044
Manic-depressive psychosis.....	102	26	25.5	± 0.042
Dementia paralytica.....	130	30	23.1	± 0.037
Normal subjects.....	250	41	16.4	± 0.022
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis.....				2.30
Schizophrenia : dementia paralytica.....				2.88
Schizophrenia : normal subjects.....				4.72
Manic-depressive psychosis : dementia paralytica.....				0.42
Manic-depressive psychosis : normal subjects.....				1.90
Dementia paralytica : normal subjects.....				1.49

As a final control—in a sense supplementary to the sample of normal subjects just described—the life expectancy tables of the United States Bureau of the Census were consulted. An effort was made to discover from them the extent to which the incidence of sibling deaths for the present subjects agreed with the general expectancy of such deaths for the whole population. This control was designed to bring out any difference there might be between the schizophrenic and the other groups when the sibling deaths actually found and those theoretically expected were compared.

RESULTS OF STUDY

From the data yielded by the case records and the questionnaires the percentage of subjects with sibling deaths as previously delimited was ascertained. The results are presented in table 2. The schizophrenic patients clearly had more brothers and sisters who died than did any of the other groups, the percentage being 39.5. On further analysis of

1. These institutions cooperated generously in this study.

2. Faris, R. E. L., and Dunham, H. W.: *Mental Disorders in Urban Areas*, Chicago, University of Chicago Press, 1939.

the data, the various subtypes did not appear to be significantly differentiated in this connection, though the groups involved were too small for statistical reliability. The value for the schizophrenic patients as a whole was 14 per cent higher than that for the group with manic-depressive psychosis. The group with dementia paralytica came next, with 23.1 per cent. The normal group was lowest, with 16.4 per cent. The critical ratios of the differences between the percentages show that the schizophrenic group varied in a statistically reliable way from both the normal group and the groups with dementia paralytica.³ The critical ratio of 2.30 between the schizophrenic group and the group with manic-depressive psychosis was more problematic. However, even here there were 98.9 chances out of 100 in favor of a real difference. There was no other critical ratio over 2.00.

As previously noted, the normal group should be scrutinized more carefully. There is a possibility that it was too heavily weighted with college students to be representative despite the rough socioeconomic matching already mentioned. In order to test this possibility, all college students were excluded from the group. Hospital attendants, unemployed men and a few Y. M. C. A. members—a total number of only 77—were now left. Of these, 15, or 19.5 per cent, showed sibling deaths, as compared with 16.4 per cent for the whole normal group. The critical ratios were the same as before. The schizophrenic patients had significantly more sibling deaths than the normal subjects (critical ratio 3.17), but there were no significant differences between the normal subjects and the other two psychotic groups. The normal sample was not, then, particularly distorted, if at all, by the inclusion of the college students in question.

Thus far the number of patients in whose family history a sibling death was encountered has been considered. It may now be noted further that any particular patient, or normal subject, might have more than 1 such death in his anamnesis. It is of interest to inquire as to the gross number of sibling deaths found among schizophrenic patients as compared with the number for other groups. The figures are given in table 3. The data show that for the 124 schizophrenic patients there were 67 sibling deaths, or 54 per hundred. For the 102 patients with manic-depressive psychosis the corresponding figures were 37 and 36 respectively; for the 130 patients with dementia paralytica, 39 and 30, and for the 250 normal subjects, 46 and 18. On this basis the schizophrenic patients were even more sharply distinguished from the other groups of subjects than when the percentage of patients with a sibling

3. In this paper a critical ratio of 2.78—McCall's criterion (How to Measure in Education, New York, The Macmillan Company, 1922, page 404)—is taken as indicating practical certainty. Such a ratio means that there are 9,973 chances out of 10,000 that there is a real difference between the groups.

death in the anamnesis was considered. The critical ratios for the differences per hundred between the schizophrenic and the other groups were all high. The only questionable ratio, again, concerned that for the schizophrenic patients and the patients with manic-depressive psychosis—a result which is substantiated by the significant difference further found between patients with manic-depressive psychosis and normal subjects. This fact will be considered in the interpretation of the results.

If a sibling death is interpreted as having a given effect on survivors, the present results may point to a-reinforcing factor, since they show not only that more schizophrenic patients have a sibling death in their anamnesis but that they have a considerably higher per hundred rate of such deaths than do other groups. In the sequel, however, it will for the most part be the percentage of patients with sibling deaths rather than

TABLE 3.—*Total Number of Sibling Deaths*

Group	Number of Subjects	Number of Sibling Deaths	Number per Hundred Subjects	Standard Deviation
Schizophrenia.....	124	67	54	± 0.045
Manic-depressive psychosis.....	102	37	36	± 0.048
Dementia paralytica.....	130	39	30	± 0.040
Normal subjects.....	250	46	18	± 0.025
Critical ratios of differences per hundred:				
Schizophrenia : manic-depressive psychosis.....				2.73
Schizophrenia : dementia paralytica.....				4.00
Schizophrenia : normal subjects.....				6.93
Manic-depressive psychosis : dementia paralytica.....				0.97
Manic-depressive psychosis : normal subjects.....				3.33
Dementia paralytica : normal subjects.....				2.56

the number of sibling deaths per hundred patients in a group which will be alluded to, since it is the extent of this type of event rather than its concentration which must in the first instance be given attention.

The fact that schizophrenic patients had a sibling death in their anamnesis significantly more often than did normal subjects or patients with dementia paralytica, and considerably more often than did patients with manic-depressive psychosis, has now been presented. It becomes necessary to inquire as to possible extraneous variables which may account for this difference.⁴ One possible factor of this sort is average

4. In view of the decreasing mortality rates for recent years, it should perhaps be considered in passing whether any error from this source is present in the results. The mean age expressed in years for each of the groups of subjects was as follows: schizophrenic patients, 28; patients with manic depressive psychosis, 46; patients with dementia paralytica, 45, and normal subjects, 26. From these figures it is easy to deduce that if an experimental error due to change in mortality rates is present, it must be reflected in the data for the subjects with manic-depressive psychosis and dementia paralytica, who were about 20 years

family size, for it is obvious that persons from larger families would have more chances of a sibling death. Table 4 presents the mean family sizes of the various groups of subjects for all cases in which this information was obtainable and shows that the schizophrenic patients did in fact come from the largest families. The mean number of siblings was 5.7. The average number for patients with dementia paralytica was 5.3, and for the patients with manic-depressive psychosis and the normal subjects the means were 4.7 and 3.7 respectively. The critical ratios between the various means indicate that the normal group had significantly fewer siblings per subject than any of the psychotic groups. This result suggests that though the normal group might be close to the psychotic groups in economic status, the college subgroup possibly represented a selection on the basis of small families. There was no

TABLE 4.—*Mean Number of Siblings in the Families of the Various Groups of Subjects*

Group	Mean Number of Siblings	Standard Deviation of Mean
Schizophrenia.....	5.7	± 0.0277
Manic-depressive psychosis.....	4.7	± 0.295
Dementia paralytica.....	5.3	± 0.250
Normal subjects.....	3.7	± 0.135
Critical ratios of differences:		
Schizophrenia : manic-depressive psychosis.....		2.44
Schizophrenia : dementia paralytica.....		1.05
Schizophrenia : normal subjects.....		6.45
Manic-depressive psychosis : normal subjects.....		3.03
Dementia paralytica : manic-depressive psychosis.....		1.51
Dementia paralytica : normal subjects.....		5.52

significant difference in this respect between schizophrenic patients and patients with dementia paralytica or between the latter and the patients with manic-depressive psychosis. There is, however, a strong indication (critical ratio 2.44) that the patients with manic-depressive psychosis had fewer brothers and sisters than the schizophrenic patients.

It having thus been found that schizophrenic patients do come from larger families, it becomes necessary to test whether the incidence of sibling deaths is greater among schizophrenic patients when the size of the family is controlled.

older than the others, and would make for a death incidence somewhat too high for comparative purposes. Since, however, the death incidences for these control psychotic groups were definitely lower than the mortality rate for the experimental group of schizophrenic subjects—and in this lies the point of the comparison—any such possibility of error must be construed as having attenuated the reported differences. The difference between the schizophrenic and the normal group, on the other hand, is so small as to be negligible.

Table 5 gives the percentage of sibling deaths for each family size in every group. (In a few instances the size of the family could not be ascertained, and these cases had therefore to be omitted.) In general the schizophrenic patients appeared to have the highest percentages of sibling deaths regardless of family size. There were only two points at which the figures for the schizophrenic group fell much lower than the percentages for the other groups. One was at the 2 sibling level, where

TABLE 5.—*Percentage of Sibling Deaths According to Size of Family*

Family Size	Schizophrenia		Manic-depressive Psychosis		Dementia Paralytica		Normal Subjects	
	Number of Patients	Percentage with Sibling Deaths	Number of Patients	Percentage with Sibling Deaths	Number of Patients	Percentage with Sibling Deaths	Number of Subjects	Percentage with Sibling Deaths
1	5	..	10	..	9	..	33	..
2	8	0	5	0	11	0	51	16
3	19	16	16	6	12	0	49	16
4	22	41	10	10	18	6	33	13
5	17	59	10	30	16	31	29	10
6	14	14	16	21	8	38	23	30
7	7	43	12	33	14	29	13	38
8	8	56	2	50	14	46	7	29
9	9	67	8	50	6	67	1	0
10	4	75	2	50	3	67	3	67
11	2	100	0	..	1	0	0	..
12	1	100	2	100	4	75	0	..
13	4	75	2	100	1	100	1	0
14	0	..	1	100	0	..	0	..
15	1	0	0	..	0	..	0	..
16	1	100	0	..	0	..	0	..

TABLE 6.—*Percentage of Subjects with Sibling Deaths in Families of Two to Six Children*

Group	Number of Subjects	Number with Sibling Deaths	Percentage with Sibling Deaths
Schizophrenia.....	80	24	30
Manic-depressive psychosis.....	57	7	12
Dementia paralytica.....	65	9	14
Normal subjects.....	190	31	16

none of the psychotic groups showed a sibling death. The normal subjects here showed 16 per cent. The other point was at the 6 sibling level, where the percentage of sibling deaths for schizophrenic patients fell to 14. Because of the large percentages immediately above and below this level, the last figure may perhaps be regarded as a chance fluctuation.

Since the number of cases for each family size is small, it is desirable to reduce the subdivisions by grouping. Families of 6 children or less may be considered first. Families with only 1 child naturally are excluded here. The results are presented in table 6, from which it appears that the schizophrenic group had 30 per cent sibling deaths while the group

with manic-depressive psychosis and the group with dementia paralytica showed 12 and 14 per cent respectively. The normal group had 16 per cent.

Families of 2, 3 and 4 children may next be examined. These family sizes are smaller than the average in any of the psychotic groups. The results are given in table 7. The schizophrenic patients, again, had the largest percentage of sibling deaths, 24, as compared with the group with manic-depressive psychosis, with 7, the group with dementia paralytica, with 2, and the normal group, with 15.

Another method for controlling the size of family and patient's position in the family was suggested by Dr. Forrest E. Linder,⁵ of the United States Bureau of the Census. This procedure utilizes a publication of the Bureau of the Census⁶ for determining the probability that at least 1 sibling will die in the family of any given subject after that subject's birth but before he is 19 years old. The method consists essentially in calculating the probability of the death of each sibling

TABLE 7.—*Percentage of Subjects with Sibling Deaths in Families of Two to Four Children*

Group	Number of Subjects	Number with Sibling Deaths	Percentage
Schizophrenia.....	49	11	24
Manic-depressive psychosis.....	31	2	7
Dementia paralytica.....	41	1	2
Normal subjects.....	138	21	15

in a hypothetical family of the same size and sibling configuration as the subject's family and then determining the total probability of at least 1 such death in the family.⁶ Linder's method was slightly modified in its application here to make it practicable for the data on psychotic patients, for it was not always possible to ascertain the exact ages of their individual siblings. The spacing between children was accordingly assumed to be two years in all cases and in all groups. Moreover, only the life tables for males were used.⁷ To eliminate the effects of extremely large families and of only children, the subjects coming from families of from 2 to 9 siblings were alone considered. The results obtained with this life table method were compared with those given by the actual examination of the case records to determine how closely the samples employed in the present study were representative of the

5. Dr. Linder gave helpful suggestions in the present connection and made a critical reading of the manuscript. For details of the method see the appendix.

6. Vital Statistics—Special Reports, 1930, United States Department of Commerce, Bureau of the Census, 1936, vol. 1, no. 20, pp. 389-399.

7. The validity of the two foregoing modifications is considered in the appendix.

total population of the United States in mortality rates. Any isolated deviation might indicate that the sample in question represented a unique frequency of sibling deaths.

Table 8 presents the figures empirically obtained as compared with those to be expected from the life tables. Of the 211 normal persons falling within the prescribed range of family sizes, 37.1, or 18 per cent, would be expected to have had sibling deaths. In actuality they had 38, or 18 per cent. The agreement is exact. The agreement for the figures for the group with dementia paralytica and that with manic-depressive psychosis is nearly as close. For the 99 in the former group, 28.7, or 29 per cent, would be expected, whereas 23, or 23 per cent were found empirically. For the 79 in the latter group, 20.3, or 26 per cent, would be expected, while 18, or 23 per cent, were actually found. The differences between the theoretic expectations and the empiric findings for these two groups are therefore small, — 6 and — 3 per cent respectively,

TABLE 8.—*Number of Subjects Expected and Found to Have Sibling Deaths*

Group	Total Number of Subjects	Number Expected	Percentage Expected	Number Found	Percentage Found	Percentage Difference
Schizophrenia.....	104	24.8	24	38	37	+13
Manic-depressive psychosis..	79	20.3	26	18	23	— 3
Dementia paralytica.....	99	28.7	29	23	23	— 6
Normal subjects.....	211	37.1	18	38	18	0

and indicate that slightly fewer deaths were found in the case records than would be expected from the life tables. Of the 104 schizophrenic patients, however, 24.8, or 24 per cent, would be expected to have had sibling deaths associated with them, whereas 38, or 37 per cent, actually did have. Here the difference is + 13 per cent, a result showing that this group of subjects had considerably more sibling deaths than would be expected from the life tables and that the deviation thus probably represents a unique rate. This finding is the more striking because the other three groups, by their close agreement between expected and actual figures, tend to support the validity of this method for controlling family size and the patient's position in the family.

It may be concluded from the two foregoing methods of controlling family size—one based on matching for number of siblings and the other utilizing life table expectancies—that schizophrenic patients appear to have more sibling deaths in their life histories up to the age of 19 years than do the other groups of subjects, regardless of the number of siblings in the family. It is not possible to account for the discovered difference in frequencies of sibling deaths on the basis of family size.

Another variable which must be considered in evaluating the results on sibling deaths is the socioeconomic status of the various groups. Since all of the patients in the study were drawn from one state hospital, it was considered that they were representative of approximately the same level in this regard. It will be recalled that an effort was also made to evaluate the extent to which the normal subjects resembled the patients in socioeconomic status by reference to monthly rentals, and it appeared that a rough similarity existed. However, the degree to which the various groups of subjects were matched on this point cannot be regarded as completely adequate, and further investigation should direct itself toward a better control of this factor. In the meantime it must be borne in mind that by the psychodynamic interpretation shortly to be considered the lower socioeconomic levels might through their higher death rate more readily provide one of the very conditions necessary for the development of schizophrenia. Whether such deaths are truly determinative can, however, be ascertained only by a study of families of schizophrenic patients and control families in the higher socioeconomic levels, in which a significantly greater frequency of deaths for the schizophrenic than for the other groups could not possibly be attributed to economic conditions and would point unambiguously to some selective aspect of schizophrenia itself.⁸

Having considered the possible effect of extraneous variables on the observation that schizophrenic patients have a significantly high incidence of sibling deaths in their life histories, such qualifying information about these deaths as is available may now be presented.^{8a} The first point of this kind concerns the sex of the dead siblings. The data on the 56 dead siblings of schizophrenic patients for whom the required sex designation could be obtained showed that 30, or 54 per cent, were

8. Though the results of the present study converge at this point with those of Faris and Dunham,² it is unfortunate that their data are not sufficiently comparable to permit of any significant conclusions. While emphasizing that schizophrenia tends to increase as one approaches the more disorganized ecologic areas of their investigation, they fail to bring this fact into relation with an almost identically parallel trend in the death rate, as shown in table 76 in their book. Possibly their concept of "isolation" is intended to cover the latter relationship by implication, but from the standpoint of the present study there arises the question whether this relation did not deserve a much more prominent place in their analysis. For it is conceivable that this relationship between death rate and ecologic area specifies an important constituent of "isolation" in the same manner as the presence of the *Anopheles* mosquito is a more specific condition for the incidence of malaria than is a swampy, hot habitat.

8a. Such qualifications regarding the deaths of the normal subjects are not given, since the interest of the study was obviously limited to the deaths in the schizophrenic group. Comparison with the other subjects was necessary for control purposes only where the statistical significance of the frequency of deaths in the schizophrenic group was in question.

males and 26, or 46 per cent, were females. In statistical terms, therefore, the sex of the dead siblings cannot be regarded as having any significance.

Another matter of interest is the patient's position in the family. Though it has been shown by Malzberg⁹ that position in the family does not in general correlate with incidence of psychosis, it seemed worth while to inquire whether some such relationship might not exist in the present, more specialized situation. Concretely, the attempt was made to ascertain whether the schizophrenic patients with sibling deaths fell more frequently in the upper or the lower half of the family. It was found that 72 per cent belonged in the former and 28 per cent in the latter position.

Further information in the same connection is found in the answer to the question whether the patient was more often older or younger than his dead brother or sister. In this inquiry it was necessary to count all dead siblings (but only those for whom the necessary information could be obtained), since it was impossible to tell which sibling death to select for a given patient. In some instances the same patient had, accordingly, to be included more than once in the calculations, and the results are therefore open to some question. What they show is that of the 61 dead siblings considered, 47, or 77 per cent, were younger while 14, or 23 per cent, were older than the patient. The preceding result is thus corroborated.

A further problem concerns the age of the schizophrenic patient at the time of the sibling death. In view of the generally recognized psychologic vulnerability of the child, it seemed well to inquire as to the proportion of sibling deaths which occurred while the subjects were very young. The number of sibling deaths taking place before the subject's sixth year of life was accordingly determined. Here, again, as with the preceding data, it was necessary to count all dead siblings (but only those for whom the required information could be obtained), so that the figures are not completely consistent with those presented earlier. It was found that of the 61 sibling deaths for the 118 schizophrenic patients, 34, or 56 per cent, occurred before the patient was 6 years old—a six year span—while 27, or 44 per cent, occurred between the patient's sixth and nineteenth year—a thirteen year span. There is thus a clear tendency for these deaths to concentrate in the early childhood years of the patient—a fact which may represent an important qualification of these events from the standpoint of psychologic experience.

The data on sibling deaths having thus been presented, some supplementary observations on the death of parents may now be considered.

9. Malzberg, B.: Is Birth Order Related to the Incidence of Mental Disease? *Am. J. Phys. Anthropol.* **24**:91-104, 1938.

The relationship between psychosis and parental death has been previously investigated by Barry¹⁰ and by Barry and Bousfield.¹¹ Barry's study was of a historical nature, showing that twice as many insane as sane kings had lost their fathers early in life. Barry and Bousfield determined the percentage of a group of 1,500 psychotic persons who had lost either parent by the age of 12 years. They found that 27.6 per cent had experienced such a death, as compared with 20 per cent for normal control data. No differentiation among the psychoses was made in their study.

TABLE 9.—*Paternal, Maternal and Parental Deaths Among Psychotic and Normal Subjects*

Group	Number of Subjects	Number with Death of a Parent	Percentage	Standard Deviation of Percentage
Paternal Deaths				
Schizophrenia.....	117	25	21	± 0.037
Manic-depressive psychosis.....	95	9	10	± 0.030
Dementia paralytica.....	112	14	12.5	± 0.032
Normal subjects.....	164	19	12	± 0.024
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis.....				2.29
Schizophrenia : dementia paralytica.....				1.73
Schizophrenia : normal subjects.....				2.05
Maternal Deaths				
Schizophrenia.....	116	8	7	
Manic-depressive psychosis.....	96	8	8	
Dementia paralytica.....	121	8	7	
Normal subjects.....	162	4	3	
Parental Deaths				
Schizophrenia.....	117	33	28	± 0.041
Manic-depressive psychosis.....	96	17	17.5	± 0.039
Dementia paralytica.....	121	22	18	± 0.035
Normal subjects.....	164	23	14	± 0.026
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis.....				1.84
Schizophrenia : dementia paralytica.....				1.82
Schizophrenia : normal subjects.....				2.86

In the present investigation the number and percentage of paternal, maternal and total parental deaths before the subject's nineteenth year were determined for all groups separately. (In some instances, particularly among the normal subjects, the information could not be obtained, and the totals for the groups thus vary somewhat from those previously given.) The results are shown in table 9. Of the schizophrenic group 21 per cent had lost their fathers, whereas only 10 per cent of the group with manic-depressive psychosis, 12.5 of the group with dementia paralytica and 12 per cent of the normal group had had such a loss. Maternal

10. Barry, H.: Orphanhood as a Factor in Psychoses, *J. Abnorm. & Social Psychol.* **30**:431-438, 1936.

11. Barry, H., and Bousfield, W. A.: Incidence of Orphanhood Among Fifteen Hundred Psychotic Patients, *J. Genet. Psychol.* **50**:198-201, 1937.

deaths occurred infrequently—3 to 8 per cent—among the present subjects, and at no point did the groups show any particular differentiation in this respect. When parental deaths as a whole were considered, the schizophrenic groups once more had the highest incidence, 28 per cent, as compared with 17.5 per cent for the group with manic-depressive psychosis, 18 per cent for the group with dementia paralytica and 14 per cent for the normal group. Moreover, the critical ratio of the percentage difference between the schizophrenic and the normal group was now 2.86 and was thus statistically significant. The other critical ratios were all below the level of significance. The present results corroborate those of Barry and Bousfield, but indicate further that it is chiefly in the schizophrenic group that the higher incidence of parental deaths among psychotic patients is apparently found. They also show that it

TABLE 10.—*Incidence of Sibling or Parental Deaths Among Psychotic and Normal Subjects*

Group	Number of Subjects	Number with Deaths	Percentage	Standard Deviation of Percentage
Schizophrenia.....	118	72	61	± 0.045
Manic-depressive psychosis.....	96	32	33	± 0.048
Dementia paralytica.....	121	50	41	± 0.045
Normal subjects.....	164	46	28	± 0.035
Critical ratios of percentage differences:				
Schizophrenia : manic-depressive psychosis.....				4.24
Schizophrenia : dementia paralytica.....				3.12
Schizophrenia : normal subjects.....				5.79
Manic-depressive psychosis : normal subjects.....				0.85
Dementia paralytica : manic-depressive psychosis.....				1.21
Dementia paralytica : normal subjects.....				2.28

is in respect to paternal rather than to maternal deaths that the higher incidence appears.

The results on parental deaths may now be considered in association with those on sibling deaths. According to the combined results, presented in table 10, 61 per cent of the schizophrenic group had either a sibling or a parental death before the age of 19 years.

The corresponding figure for the group with manic-depressive psychosis was 33 per cent, for the group with dementia paralytica 41 per cent and for the normal group 28 per cent. Here for the first time every critical ratio for the difference between the schizophrenic and each of the three control groups is statistically significant—5.79 for the normal group, 4.24 for the group with manic-depressive psychosis and 3.12 for the group with dementia paralytica. None of the other critical ratios reach the level of statistical significance.

It may, then, be concluded that in the life histories of male schizophrenic patients immediate familial deaths before the patient arrives at the nineteenth year are found significantly more often than is true of patients with manic-depressive psychosis or dementia paralytica or of

normal subjects. The schizophrenic subtypes do not appear to be particularly differentiated in this respect. Of the patients studied, 61 per cent showed a sibling death, a parental death or both. Sibling deaths distinguished the schizophrenic patients much more sharply from the control groups than did parental deaths. The sibling deaths, which were found in 39.5 per cent of the anamneses, usually involved persons younger than the patient and occurred more often than not before the patient's sixth year. The dead siblings were as often males as females. Such extraneous factors as family size and family configuration do not appear to account for the sibling death figures, but it should be added that until a larger number of subjects has been studied, particularly female patients, and the factor of socioeconomic status has been more fully controlled, the present results must be regarded as indicating merely a strong presumptive trend.

INTERPRETATION

On the assumption that it is generally true, as has been shown for the patients in the present study, that schizophrenic patients more frequently have sibling deaths in their life histories than do other persons, the question of explanation naturally arises. Three possible avenues of theoretic interpretation appear to be open.

1. The first, and in some senses the simplest, view of the matter is that the families of which schizophrenic persons are members suffer from a general constitutional weakness that manifests itself concomitantly in the occurrence of many sibling deaths and in the schizophrenic disease process. This may be called the somatogenic view. Such an interpretation would accord with certain direct, though fragmentary, evidence and with a more or less generally held opinion that schizophrenia is rooted in a constitutional predisposition. No evidence in addition to that already given can be offered here either in proof or in disproof of this hypothesis. A possible approach to the problem in future study lies in the relationship which some investigators believe to exist between the tuberculous and the schizophrenic diatheses.¹²

2. While the somatogenic view tends to relegate both the sibling deaths and the schizophrenic disease process to a common cause, and thus makes them essentially independent of each other, a second possible interpretation might regard these two facts as interdependent, the sibling death serving as a basis for the schizophrenic process. By placing chief

12. Lewis, N. D. C.: *The Constitutional Factors in Dementia Praecox*, Nervous and Mental Disease Monograph 35, New York, Nervous and Mental Disease Publishing Company, 1923. Luxenburger, H.: *Tuberkulöse als Todesursache in den geschwisterschaften Schizophrener, Manisch-Depressiver und der Durchschnittsbevölkerung*, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:313-340, 1927; *Ueber weitere Untersuchungen zur Frage der Korrelation von schizophrene Anlage und Widerstandsschwäche gegen die tuberkulöse Infektion*, *ibid.* **122**:74-89, 1929.

stress on the psychologic effects of the sibling death as experienced by the surviving sibling, this view goes to the other extreme from that of the somatogenic and may therefore be called the psychogenic interpretation. In its context are relevant the observations of Freud¹³ as to the potentially powerful effects of the father's death and the hypothesis of Zilboorg¹⁴ that the death of close relatives or friends in the early life experience of a person may serve as a basis for later suicidal tendencies. It may be noted that it was such psychologic aspects of the problem that, in the study of several individual patients, first drew attention to the possible significance of sibling deaths in schizophrenia.

The psychogenic interpretation would begin by pointing to the great importance of sibling rivalry. From the psychoanalytic standpoint such rivalry is essentially a struggle to gain or to retain the love of the mother in the earliest years of life. It is thus in certain respects similar to the Oedipus situation, in which the male child is a rival of the father for the mother's love. If, now, with reference to the data of the present study, a male child who is firmly entrenched in the mother's love is thought of as suddenly confronted with a sibling that threatens to displace him, intense hostility may be presumed to develop. Rivalry would not be limited necessarily to sibling displacement, since it might be felt toward an older sibling also, but it would probably be maximal when the rival was a newcomer. In any case the hostility involved may be supposed to extend, where the young child is concerned, even to death wishes. In most instances there would exist along with such hostile trends strong libidinal components from various sources. For example, if the displacing sibling were a female, she might in some respects serve as a surrogate for the mother and atone, as it were, for her rivalry by offering the male sibling some degree of feminine love herself. If the rival sibling were a male, he might serve as a father surrogate and help mediate the solution of the Oedipus problem by the establishment of homosexual bonds. But whatever the source of such libidinal accompaniments of the hostility in sibling rivalry, the outcome would be the same: a highly ambivalent relationship between the siblings. It is on such intense ambivalence that any extreme effect of the sibling death would probably depend in the end.

With such a background—intense hostility to the displacing sibling, complicated in some degree by contravalent libidinal trends—let it now be supposed that the rival sibling dies. The hostile wishes against the rival would even in his lifetime have been accompanied by a counter-

13. Freud, S.: *Interpretation of Dreams*: Authorized Translation of Third Edition with Introduction by A. A. Brill, London, Allen & Unwin, 1913.

14. Zilboorg, G.: *Differential Diagnostic Types of Suicide*, Arch. Neurol. & Psychiat. **35**:270-291 (Feb.) 1936.

part of guilt feelings. The latter would be all the more intense if the hostility was directed toward some one who was at the same time loved. Now that the death wishes have, as if by magic, been realized the guilt feelings would become maximally acute.

The significance of sibling rivalry as thus portrayed has been described by numerous writers. Among these may be mentioned Flügel,¹⁵ Klein¹⁶ and Levy.¹⁷ The extent of the hostility engendered by such rivalry has been shown by them to be very great, including death wishes and even acts of fatal violence. Bender and Curran,¹⁸ in a recent report, have given striking examples of children and adolescents who have attempted, successfully or unsuccessfully, to carry out such wishes. More frequently, however, the wishes are not acted on but are important chiefly because they are accompanied by intense feelings of guilt or because events may accidentally bring about their fulfilment in a way that must appear almost magical to the child. In this contingency the guilt feelings which usually form the counterpart of death wishes are, as Feigenbaum¹⁹ has shown, greatly magnified. Schilder and Wechsler²⁰ concluded from their investigation that the child conceives of death as resulting always from violence and as not necessarily being final. The dead are not gone forever. These observations make it easy to see how a surviving brother or sister could interpret the death of a sibling as having been the result of his or her hostility rather than of natural causes and might, furthermore, look forward to the return of the deceased in a fashion tending to keep the experience of the death alive. Such an expectation would be enhanced by the reparation trends, which as an assuagement of anxiety are generally found to accompany the child's destructive tendencies.

The guilt feelings and anxiety of the surviving sibling might exist, as has already been indicated, in various forms and blends. The particular ambivalent character of the sibling relationship would determine these patterns. If the libidinal components of the attachment had been strong, the guilt would in some measure be increased by feelings of unworthi-

15. Flügel, J. C.: *Psychoanalytic Study of the Family*, London, Hogarth Press, 1935.

16. Klein, M.: *Psycho-Analysis of Children*, translated by A. Strachey, New York, W. W. Norton & Company, Inc., 1932.

17. Levy, D.: *Studies in Sibling Rivalry*, Research Monograph 2, New York, American Orthopsychiatric Association, 1937.

18. Bender, L., and Curran, F. J.: *Children and Adolescents Who Kill*, J. Crim. Psychopath. **1**:297-322, 1940.

19. Feigenbaum, D.: *Paranoia und Magie*, Internat. Ztschr. f. Psychoanal. **16**:363-369, 1930.

20. Schilder, P., and Wechsler, D.: *The Attitudes of Children Toward Death*, J. Genet. Psychol. **45**:406-451, 1934.

ness—for having killed the one from whom love had been received. If any degree of tabooed sexual activity, or even fantasy, entered into the relationship another source of guilt would be tapped. Mourning for the lost object might also combine with the guilt feelings springing from hostility. But the driving power of the reaction would stem from the guilty knowledge that the hostile death wishes had taken effect.

The consequences of such guilt would theoretically be of two kinds, each resembling a different main aspect of the schizophrenic reaction pattern. In the first place, the surviving sibling would be prevented by his isolative guilt and the underlying fear of his externalized aggression (and libido) from making normal social contacts. These inhibitions would affect relationships within and, even more so, outside the family. In the normal development of the person, as has been repeatedly pointed out, conditioning first acquired within the family serves by transfer as a basis for extrafamilial associations. The guilt resulting from the sibling death might thus disrupt the normal transfer of social patterns and serve as a source of the asocial schizophrenic reaction type. When the sibling attachment had involved strong components of love, which would now be linked with the guilt feelings due to the death, libidinal object relationships would likewise be impaired. Hence, both the general asociality of the schizophrenic person and his usual incapacity for libidinal object attachments could in part be traced to the consequence of having experienced a sibling death.

A second consequence of the guilt reaction in the surviving sibling may be regarded as a complement of the first. Whereas the first emphasizes negative behavior—withdrawal from social intercourse—the second points to positive manifestations of a substitutive character. That is, the void created by the death of the sibling, and even more so by the withdrawal from society, begins now to be filled with fantasies that provide substitute satisfactions and tend to stabilize the reactions of the person at an asocial level. Thus would arise autistic, bizarre mannerisms, hallucinations and delusions traceable in greater or less degree to the effects of the sibling death.

The result of these two cooperating tendencies would in the paradigmatic case be the very characteristics of the schizophrenic patient as clinically observed: marked incapacity for social contacts; inadequacy in libidinal object relationships; positive manifestations of a fantastic kind, including hallucinations and delusions, and a strong underlying sense of guilt and anxiety associated with repressed hostility.

That this second, or psychogenic, interpretation is consonant with the results of the present study is clear. It has been shown that the schizophrenic patients came in most instances from the upper half of

their families and that in the majority of cases the dead siblings met their fate before the patient's sixth year of life. These two facts cooperate to emphasize that the schizophrenic patient as a surviving sibling was in the acute rivalry position of having been displaced by a new claimant on the mother's love and that the death of the rival usually occurred in the important formative years of childhood.

If it is recalled that the present study is concerned with male patients only, it will be seen that the interpretation is borne out also by the facts on parental deaths. On the one hand, the father would, like a sibling, represent for such a patient a rival for the mother's love. It would, accordingly, be expected that the incidence of paternal deaths might—as was actually found—be high among patients with schizophrenia. On the other hand, again as actually found, maternal deaths would not play a significant role. However, with the limited data now available, and in advance of a similar study on female schizophrenic patients, the parental deaths cannot be emphasized in the interpretation.

3. According to a third possible view, which combines the preceding two, a constitutional weakness may contribute concomitantly to the sibling deaths and to the schizophrenic disease process. But just as in the case of the deaths the environment would provide certain specific noxae, e. g., microbes, to effect the result, so in the production of schizophrenia traumatic psychologic experiences, such as sibling deaths, would cooperate. A peculiarity of this view is that in relation to schizophrenia the sibling deaths might count twice—once as causally rooted in the common constitutional weakness and again as having traumatic psychologic effects. In other words, the families of schizophrenic patients are weak in constitution and hence suffer many early deaths. On a similar basis, the prospective schizophrenic patient is from birth less active and independent than other persons. He would thus have more than the average sensitivity to siblings and parents and become abnormally attached to them. Intense feelings of hostility and love toward siblings would therefore more readily develop; guilt feelings and anxiety after sibling deaths would be similarly greater. At this point the psychogenic hypothesis presented in the preceding section would apply to complete the interpretation.

This view may be designated as psychosomatic and would, in keeping with present knowledge, seem to be the closest to the truth of the three discussed in this section. It steers a middle course between the two extremes and appears to reconcile them. Even more important is the fact that it sets the stage for further investigation on schizophrenia by a technic which should make it possible to penetrate more deeply than hitherto into the recognizedly specious dichotomy of constitution and experience.

CONCLUSION AND SUMMARY

It must be apparent that from a psychodynamic orientation deaths of other persons besides siblings could serve to produce similar effects. Presumably, parental deaths and, in the present study especially paternal ones, are to be so regarded. The deaths of other close relatives or intimate friends should likewise be considered. Moreover, the type of frustrating experience or deprivation need not necessarily be limited to death. The clinically recognized effect on the growing child of broken homes might, for example, work out similarly. The present study has thus singled out one factor in a psychodynamic class and will, it is hoped, serve to stimulate systematic investigation of some others.

It should also be noted that the disorder resulting from sibling death and cognate frustrating experiences cannot necessarily be limited to schizophrenia. The present data themselves seem to indicate that manic-depressive psychosis is apt to have such factors in the anamnesis, whereas dementia paralytica, for example, does not. In addition, individual cases could have been readily adduced to show how sibling death has apparently been involved in disorders such as epilepsy. Here, too, lies a problem for more extensive research.

For the present, however, conclusions must be limited to schizophrenia, and here it may be said, on the basis of the data from the 356 adequate individual histories studied, that male schizophrenic patients have up to twice as great a chance (39 per cent) of experiencing sibling deaths as do certain control groups (patients with manic-depressive psychosis and dementia paralytica and normal subjects). This observation holds even when extraneous factors, such as size of family, have been statistically controlled. The majority of such deaths occur in siblings younger than the patient and previous to the patient's sixth year of life. When parental deaths are considered together with sibling deaths, it is found that 61 per cent of the schizophrenic patients had one or both in their history. They are in this respect differentiated from all three control groups with statistical significance. Nevertheless, these results must be considered tentative till more subjects, especially females, have been studied.

The interpretation of the results on sibling deaths that seems to accord best with current knowledge is a psychosomatic one, in which a possible constitutional weakness is regarded as having been acted on by disrupting psychologic experience. On the basis of a strong hostility to the sibling that dies—whether founded primarily on rivalry or on ambivalent libidinal trends with intense aggressive components—guilt is acutely intensified in the surviving sibling by the death. A groundwork is thus laid for a disturbance of the normal transfer of social patterns from the familial constellation to the extrafamilial milieu

and for a complementary tendency toward filling the social void with substitutive fantasies. In such a context sibling deaths may be construed as one factor in the production of schizophrenic reaction patterns.

APPENDIX: METHOD FOR DETERMINING THEORETIC PROBABILITY OF SIBLING DEATHS

The method in question is best described in Dr. Forrest E. Linder's own words:

"Suppose, for example, that one is interested in a subject who was born in a given year. It may be assumed that fifteen years after his birth a male sibling was born. When the subject has reached his twenty-fifth year, the sibling will then have reached his tenth year. The question, then, is: 'What is the chance that the younger brother will have died during his possible ten years of life?' To obtain an answer to this question, one looks in column 3 of the life table published by the United States Bureau of the Census,⁶ page 392, which gives the expected number who will die out of 100,000 persons starting life. On adding the first ten figures in this column one gets a total of 8,859. That means that out of 100,000 persons starting life, 8,859 will have died. The probability of this sibling's death, therefore, will be 0.08859 ($p_1 = 0.08859$). That is the probability for a family of 2 male children of the specified age distribution (family 1).

"Now consider the case of a larger family (family 2). In this family it may be assumed that the subject in whom one is interested was born on a given date and that his first younger brother was born fifteen years later. Then the probability of this first brother's dying is the same as that of the sibling in the family previously discussed; that is, $p_1 = 0.08859$. It may now be assumed that the second younger brother was born twenty years after the subject. Then, at the time the subject has reached the age of 25 years, the second younger brother will have reached the age of 5 years. What is the probability that the second younger brother will have died? On adding up the first five entries in column 3 one finds the probability of death to be expressed by the formula $p_2 = 0.07931$. The probability that each brother separately might have died has now been found. What is the probability that either one or the other will have died? To find this, one must compute the probability that each brother will not have died, using the formulas: $q_1 = 1 - p_1$, or 0.91141 and $q_2 = 1 - p_2$, or 0.92069. The probability, then, that both brothers will live is equal to $q_1 \times q_2$, which in my example equals 0.8391. Hence the probability that both younger brothers will not live, that is to say, the probability that at least one will have died, is computed as follows: $p_3 = 1 - q_1 q_2$, or 0.1609. The way to proceed from here is to observe a random sample of hospital patients

of the diagnostic type in which one is interested without, however, paying any regard to sibling deaths. For each one of these families computations similar to the foregoing ones are made. A tabulation similar to the one which follows can then be constructed:

<i>Family</i>	<i>Probability of Sibling Death</i>
Family 1.....	0.08859
Family 2.....	0.1609

"The total for the last column ($\sum p_1$) will give the number of deaths to be expected in all the families under observation. The variance will be $\sum p_1 (1 - p_1)$. Naturally, if there is more than one family of the same composition, each instance of that family type must be entered in the table as a separate figure. The figure obtained in this way should give an estimate of the expected number of families with one or more deaths if the deaths are occurring according to the life tables of the United States Bureau of the Census. This is not the expected number of deaths. Then, if in the observed sample one actually finds more than the expected number of families, there would be some evidence to substantiate the hypothesis that sibling deaths are a contributing factor in the psychosis.

"In making the foregoing computations, one should note that separate tables are given for white males, white females, Negro males and Negro females. Life tables, of course, vary considerably from state to state and according to economic status and other factors. If these qualifying factors are not provided for in the computations, they of course stand as variables which leave the result in some question."

As noted in the text, the method suggested by Dr. Linder was somewhat modified in its present application. The validity of these variations may be briefly considered. The assumption of a uniform two year spacing between children was necessary because in the data on psychotic patients it was not always possible to ascertain the exact ages of the siblings. Nevertheless, this assumption required testing. Since the normal group contained many small families, the average spacing might well have been greater there. Under these conditions the interval between the birth of a sibling and the nineteenth year of life might be sufficiently increased to change the expected probability of death. If present, this tendency would distort the results for the normal subjects in such a way that more deaths would theoretically be expected than was justifiable. This error would, in turn, decrease the actually appearing difference between expected and actual deaths. To test the assumption, expectancies of sibling deaths for 50 normal subjects were calculated according to actual spacing, as well as for the hypothetical two year spacing. According to the actual spacing of the 50 normal subjects

9.2, or 18 per cent, would be expected to have sibling deaths. With the uniform two year spacing the expectancy was 8.5, or 17 per cent. Thus the assumed and the actual spacing give nearly the same results for this normal group. Any possible distortion would naturally be less for the schizophrenic patients, who came from the larger families. The assumption is therefore considered valid.

The other modification, which consisted in the use of life tables for males alone, appeared justifiable because male and female sibling deaths were evenly balanced in all the groups of the present investigation and because male and female death rates were considered sufficiently similar for the present purposes.

Worcester State Hospital.

DISTRIBUTION OF IODINE IN BLOOD SERUM AND IN CEREBROSPINAL FLUID

EDWIN F. GILDEA, M.D.

AND

EVELYN B. MAN, Ph.D.

NEW HAVEN, CONN.

Conflicting reports in the literature on the amount and distribution of iodine in the blood and in the cerebrospinal fluid suggested the reinvestigation of these problems with reliable methods. The iodine contents of the serum and spinal fluid were determined for 6 patients who were free from meningeal disorders and had normal spinal fluid proteins. To a second group of 8 similar patients approximately 0.1 Gm. of inorganic iodine in the form of compound solution of iodine U. S. P. was administered daily for three to seven days before the samples of spinal fluid were obtained. Organic iodine in the form of thyroid was given instead of inorganic iodine to an additional patient. Finally, 1 patient with meningovascular syphilis and high spinal fluid proteins was studied. The recently developed permanganate acid ashing method of Riggs and Man¹ avoids the positive errors of previous methods. In addition, in serum by precipitation with zinc sulfate and sodium hydroxide the diffusible inorganic iodine was differentiated from the precipitable (protein-bound), nondiffusible iodine.² Furthermore, the determinations were made in duplicate on large aliquots of cerebrospinal fluid obtained in the preparation of patients for pneumoencephalography.

The older literature on cerebrospinal fluid iodine has been reviewed by Katzenelbogen.³ With the exception of the recent work of Klassen,

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From the Biochemistry Laboratory of the Department of Psychiatry, Yale University School of Medicine.

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2. Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: Serum Iodine Fractions in Hyperthyroidism, *J. Clin. Investigation* **21**:773, 1942.

3. Katzenelbogen, S.: *The Cerebrospinal Fluid and Its Relation to the Blood*, Baltimore, Johns Hopkins Press, 1935.

Bierbaum and Curtis,⁴ spinal fluid iodine has been estimated by older methods which either were not sufficiently sensitive or were subject to positive errors. Consequently, some authors⁵ have found considerable amounts, 10 to 20 micrograms per hundred cubic centimeters, while others⁶ have obtained the barest traces, even in patients who had been ingesting large amounts of iodine for several months. It is obvious that with this uncertainty as to methods the older data on the relation of serum iodine and cerebrospinal fluid iodine must be interpreted with caution.

METHODS

The spinal fluid used in these studies was collected from each patient when the cerebrospinal system was drained for pneumoencephalographic examination. The puncture was made in the third or fourth lumbar space, and as each 10 cc. of fluid was removed the same amount of air was injected. The first 10 cc. of fluid was taken in a separate tube for cytologic and serologic examination, and the rest was collected in a chemically clean flask for the chemical studies. No iodine was used in the preparation of the patient, and special precautions were taken to see that no iodine was free in the room air.

Iodine was determined on duplicate aliquots of spinal fluid by the permanganate acid ashing method of Riggs and Man.¹ Most aliquots were large, 20 to 80 cc., a factor which increased the accuracy of the determinations. In 4 instances smaller amounts were used, and this fact has been indicated in the table.

Proteins were measured by the Denis-Ayer⁷ method for cerebrospinal fluid proteins. The samples of blood were taken shortly before the lumbar puncture. The serum was analyzed for total iodine and protein-bound iodine by methods previously described.⁸

DATA

A variety of patients were studied, as indicated in the table. Six patients presenting various symptoms of early intellectual deterioration or unexplained convulsions, but free from meningitis, tumor of the brain or syphilis, who had not received any iodine except minute amounts in the hospital diet, constituted the

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8. Riggs and Man.¹ Man and others.²

first group. A second group of 8 similar patients were given by mouth 30 minims (2 cc.) of compound solution of iodine U. S. P. daily for two to seven days before withdrawal of their spinal fluid. One patient, case 15, with meningovascular

Comparison of Iodine in the Blood Serum and in the Cerebrospinal Fluid

Case	Age, Yr.	Serum Iodine		Spinal Fluid			Comment and Results of Pneumoencephalographic Examination
		Total, Micro-grams per 100 Cc.	Precipitable, Micro-grams per 100 Cc.	Iodine, Micro-grams per 100 Cc.	Aliquots, Cc.	Protein, Mg. per 100 Cc.	
No Iodine Administered							
1	44	5.0	...	0.2	50	16.7	Progressive degenerative cerebral disorder; cortical atrophy and dilatation of ventricles
2	26	5.6	...	0.2	50	27	Injury to left frontal region of head, followed by convulsions; dilatation of left lateral ventricle
3	28	4.9	...	0.1	60	30	Psychopathic personality; low intelligence; cortical atrophy; dilatation of ventricles
4	44	8.8	...	0.4	80	11	Intellectual deterioration; cortical atrophy
5	31	5.0	...	<0.1	35	18	Chronic headaches; multiple complaints; bilateral cortical atrophy; dilatation of ventricles
6	26	6.1	5.4	0.1	25	32	Rare convulsions; queer compulsive behavior
After Oral Administration of Compound Solution of Iodine 2 to 7 Days							
7	26	342.0	7.7	3.0	12	39	Ventricles not visualized
8	33	94.0	7.3	1.0	30	25	Repeated convulsions; bilateral cortical atrophy and dilatation of ventricles
9	55	29.0	5.9	1.6	7	48	Depressed and agitated mood with generalized tremor
10	36	121.0	5.9	2.7	9	32	Paranoid schizophrenia
11	38	303.0	5.7	11.8	30	85	Depression and failing memory; bilateral cortical atrophy; dilatation of ventricles
12	58	522.0	5.8	6.1	15	11	Cerebral arteriosclerosis; slight cortical atrophy; hydrocephalus ex vacuo
13	46	6.3	3.3	35	40	Cortical scarring after head injury, with distortion of temporal horn of left ventricle; queer apathetic behavior; diabetes mellitus
14	27	5.0*	25	42	Apathy and confusion; schizophrenia (?) ; ventricles not visualized
15	44	873.0	...	22 *	35	160	Meningovascular syphilis, positive Wassermann reaction
After Administration of Desiccated Thyroid, 10 grains (0.65 Gm.) Daily for Two weeks and 15 grains (0.975 Gm.) for Third Week							
16	50	13.9	9.6	0.5	27	23	Depression; semistupor; basal metabolic rate —15 per cent; moderate cortical atrophy

* Blood was present in the spinal fluid.

syphilis was also given compound solution of iodine. Finally, 1 patient, case 16, with stupor of unknown origin, was given desiccated thyroid, 10 grains (0.65 Gm.) daily for two weeks and then 15 grains (0.975 Gm.) for one week previous to withdrawal of cerebrospinal fluid.

RESULTS

As can be seen in the table, in the spinal fluid of patients to whom no iodine was given only traces, less than 0.1 to 0.4 microgram per hundred cubic centimeters, of iodine were found in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum. When sufficient inorganic iodine had been given to increase the serum iodine to as much as 522 micrograms per hundred cubic centimeters, only a very slight increase in iodine occurred in the cerebrospinal fluid. It is noteworthy that in the patient with meningitis, with a total iodine content of the serum of 873 micrograms per hundred cubic centimeters, considerable iodine entered the spinal fluid. Although there were red blood cells in the spinal fluid of this patient, the elevation in iodine was greater than would have been expected from the number of erythrocytes. Furthermore, in 2 patients high spinal fluid proteins tended to be associated with a high iodine content. Administration of desiccated thyroid to the patient in case 16 increased greatly the iodine in the serum but did not appreciably affect the iodine in the cerebrospinal fluid.

COMMENT

It can be concluded that only traces of iodine normally occur in the cerebrospinal fluid. The large aliquots of fluid used and the extreme sensitiveness of the method employed establish this point conclusively. These results confirm the observations of Klassen, Bierbaum and Curtis,⁴ who used a dichromate ashing method but had less fluid for analysis.

It is noteworthy that the readily diffusible inorganic iodine did not pass in any quantity from the serum into the spinal fluid. The diffusibility of serum inorganic iodine has been previously demonstrated by Riggs, Laviates and Man⁹ in the case of red blood cell and cellophane membranes. It is clear therefore that serum inorganic iodine is prevented by some barrier from passing into the spinal fluid. The experiments of Wallace and Brodie¹⁰ on dogs suggested such a barrier. They, however, used enormous amounts of iodine and employed one of the older macrochemical methods for iodine, thereby rendering uncertain the interpretation of their results in the case of human beings.

The protein-bound iodine, probably hormonal iodine, of serum showed no tendency to enter the spinal fluid, as might have been expected from the fact that it is not readily diffusible.

These results constitute further evidence of the unique nature of the cerebrospinal fluid. Chlorides resemble iodides so far as ionization

9. Riggs, D. S.; Laviates, P. H., and Man, E. B.: Investigations on the Nature of Blood Iodine, *J. Biol. Chem.* **143**:363, 1942.

10. Wallace, G. B., and Brodie, B. B.: On the Source of the Cerebrospinal Fluid: The Distribution of Bromide and Iodide Throughout the Central Nervous System, *J. Pharmacol. & Exper. Therap.* **70**:418, 1940.

and diffusion are concerned; yet they are present in larger amounts in spinal fluid than in blood serum. Iodides, on the other hand, are found only in traces in the spinal fluid and, unlike the chlorides, appear to be selectively prevented from entering the spinal fluid. In contrast to the chlorides, calcium compounds behave in a manner similar to the iodides. While present in the spinal fluid in considerable quantities, calcium seems to be selectively prevented from diffusing from serum to spinal fluid in many conditions associated with hypercalcemia, in which much of the calcium is known to be in the diffusible form.¹¹ These observations lend support to the conception of the existence of a special blood-spinal fluid barrier.

CONCLUSIONS

Only minute amounts of iodine, less than 0.1 to 0.4 microgram per hundred cubic centimeters, are present in the spinal fluid, in contrast to relatively large amounts, 4.9 to 8.8 micrograms per hundred cubic centimeters, in the blood serum.

When the inorganic iodine of serum is increased to more than 100 micrograms per hundred cubic centimeters for days or a week, only a slight rise of 1 to 6 micrograms per hundred cubic centimeters occurs in the spinal fluid unless the protein content of the cerebrospinal fluid is also elevated.

There is, therefore, a definite barrier for iodine between the serum and the cerebrospinal fluid.

These observations add further evidence indicating the unique nature of cerebrospinal fluid as compared with other body fluids. They illustrate the peculiarly selective properties of the blood-cerebrospinal fluid barrier.

Yale University School of Medicine.

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FUNCTIONAL REPRESENTATION IN THE OCULOMOTOR AND TROCHLEAR NUCLEI

MORRIS B. BENDER, M.D.

AND

EDWIN A. WEINSTEIN, M.D.

NEW YORK

The localization of function in the cell masses of the oculomotor nucleus has not been established. While allocation of pupillary constriction to the small-celled Edinger-Westphal nucleus has been generally recognized, there is still controversy regarding the representation of functions of the extrinsic ocular muscles subserved by the third cranial nerve. Tsuchida¹ stated that there was no exact localization and that the ocular muscles received their innervation diffusely from all the cell groups. The most widely accepted view is that of Brouwer,² who from a review of the literature and from a single clinicopathologic observation postulated the following cephalocaudal arrangement of functional representation of the ocular muscles within the oculomotor nucleus; (a) sphincter pupillae; (b) levator palpebrarum; (c) superior rectus; (d) medial rectus; (e) inferior oblique, and (f) inferior rectus.

This scheme of segmentation had been suggested previously by Bernheimer³ on the basis of the retrograde cell degeneration after extirpation of individual ocular muscles. There are, however, few records of physiologic investigation of the oculomotor nucleus. Hensen and Völckers⁴ electrically stimulated the periaqueductal region of a dog's brain, but they admitted that their results were not altogether satisfactory because of the lack of exact methods.

From the laboratories of the Mount Sinai Hospital.

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4. Hensen, V., and Völckers, C.: Ueber den Ursprung den Accommodationsnerven, nebst Bemerkungen über die Function der Wurzeln des Nervus oculomotorius, Arch. f. Ophth. (pt. 1) 24:1-26, 1878.

With the Horsley-Clarke stereotaxic instrument and modern stimulator devices this difficulty may be overcome so that specific and limited areas may be stimulated with minute currents. The animal most suitable for such purposes is the monkey, not only because it can be used in the stereotaxic device but because the plan of its oculomotor apparatus is so closely related to that of man. There follows a report of a correlated functional and structural study of the oculomotor and trochlear nuclei and their roots in the monkey.

METHOD

Twenty-five monkeys (*Macaca mulatta*) were studied in the Horsley-Clarke apparatus by the technic described by Ranson⁵ and Harrison.⁶ Stimulations and lesions were made with a bipolar needle electrode having a combined diameter of 0.8 mm. A pulsating, spike-shaped current was supplied through a Dumont variable frequency stimulator. The frequency was kept constant at 250 per second. The smallest electromotive force which was necessary to produce a minimal response was 12 volts according to our instrument. This threshold was equivalent to 0.8 volt on the ordinary alternating 60 cycle sinusoidal current.

Every point explored was tested with different strengths of current. Only minimal effects were considered in final analysis. Stimulations were made under very light anesthesia induced with pentobarbital sodium or ethylcarbamate. In many instances the narcosis was so light that when the stereotaxic apparatus was removed the monkey appeared to be fully awake. Stimulations were made along vertical and horizontal planes at 0.5 to 1 mm. intervals. In 1 monkey the exploration was made in an oblique plane at an angle of 15 degrees posterior to the vertical. All the monkeys withstood the operations and recovered quickly. In 4 of the animals lesions were made at designated points with electrocoagulation currents of 3 milliamperes for fifteen to thirty second intervals. The monkeys were then observed daily for oculomotor defects. Pupillary reactions were studied cinematographically under infra-red illumination and controlled light stimulation by Dr. Otto Lowenstein, at New York University.

For histologic studies, 14 monkeys were killed by an overdose of sodium pentobarbital. The points of stimulation were identified and checked against horizontal and vertical wires passed through arbitrary points. In 7 monkeys stimulations were made along both vertical and horizontal planes so that each needle tract served as an anatomic gage against the other in terms of the right-angled coordinate. Allowances were made for shrinkage after embedding in pyroxylin. Serial sections were made of each brain stem and stained by the Weil, hematoxylin and eosin and Nissl methods.

RESULTS

Effects of Stimulation.—With small currents discrete unilateral oculomotor responses were obtained by stimulating the regions of the oculomotor nucleus and roots.

When the electrode was moved down dorsoventrally in the vertical plane of the stereotaxic instrument, the first of the oculomotor responses

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obtained was ipsilateral pupillary constriction. With slightly greater currents the constriction was bilateral, but was usually more marked on the side of stimulation. Bilateral miosis was also obtained from other areas, such as the regions of the pretectum and posterior commissure, as described by Ranson and Magoun⁷ and Magoun and Ranson,⁸ and from the ventral portion of the central tegmental fasciculus. The miosis obtained from the central tegmental fasciculus in the pons is part of the lid closure reaction, in which the eyelids close and the eyeballs roll up in association with pupillary constriction.

Ventral to the focus for pupillary constriction was that for downward movement of the ipsilateral eyeball. In 1 monkey conspicuous bulging of both irises was observed on stimulation of a point at the midvertical and midsagittal planes of the body of the oculomotor nucleus. The focus was 1 mm. below that for pupillary constriction. The bulge in the iris was prominent during the entire period of stimulation and was greatest at the pupillary margin. When the current was stopped the bulge receded sharply. There was no associated convergence movement, and unless more than threshold current was used there was no pupillary constriction. It is presumed that the bulge in the iris was due to contraction of the ciliary muscle, causing the lens to become more globular and to move forward, which pushed the iris anteriorly.

The next ventral point yielded downward and inward movements. Again, this response was ipsilateral, and with increase in voltages at the same point of stimulation other ipsilateral ocular movements appeared, in the following sequence: (a) 13 volts, downward and inward; (b) 14.5 volts, inward; (c) 17.5 volts, inward and upward, and (d) 25 volts, inward and upward plus retraction of the lid. Thus by increasing the current at any one point it was possible for one to predict the response of adjacent or deeper structures. The downward and inward motion seemed to be the resultant action of the inferior and the internal rectus muscle. At times this oblique movement had an element of extorsion, but never the intorsion produced by the action of the superior oblique muscle, innervated by the fourth cranial nerve. The direction of the torsion could readily be detected by observing the movement of radiating conjunctival vessels.

One millimeter below the focus for downward and inward movement was that for pure adduction. This individual inward movement was ipsilateral and was seemingly the strongest of all effects produced by stimulation in this region of the brain stem. When the electrodes were

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8. Magoun, H. W., and Ranson, S. W.: The Central Path of the Light Reflex: A Study of the Effect of Lesions, *Arch. Ophth.* **13**:791-811 (May) 1935.

within 0.2 mm. of the midline and the current was strong enough, bilateral sharp inward rotation of the eyes occurred, but this could be distinguished from the slower bilateral convergence movements elicited from other regions.

The next ventrally situated point yielded inward and upward movement. Again, this was ipsilateral and probably the resultant action of the internal and the superior rectus muscle. On further sinking of the electrode pure upward movement of the eyeball was elicited, and 0.5 to 1 mm. below this center stimulations yielded elevation of the superior eyelid.

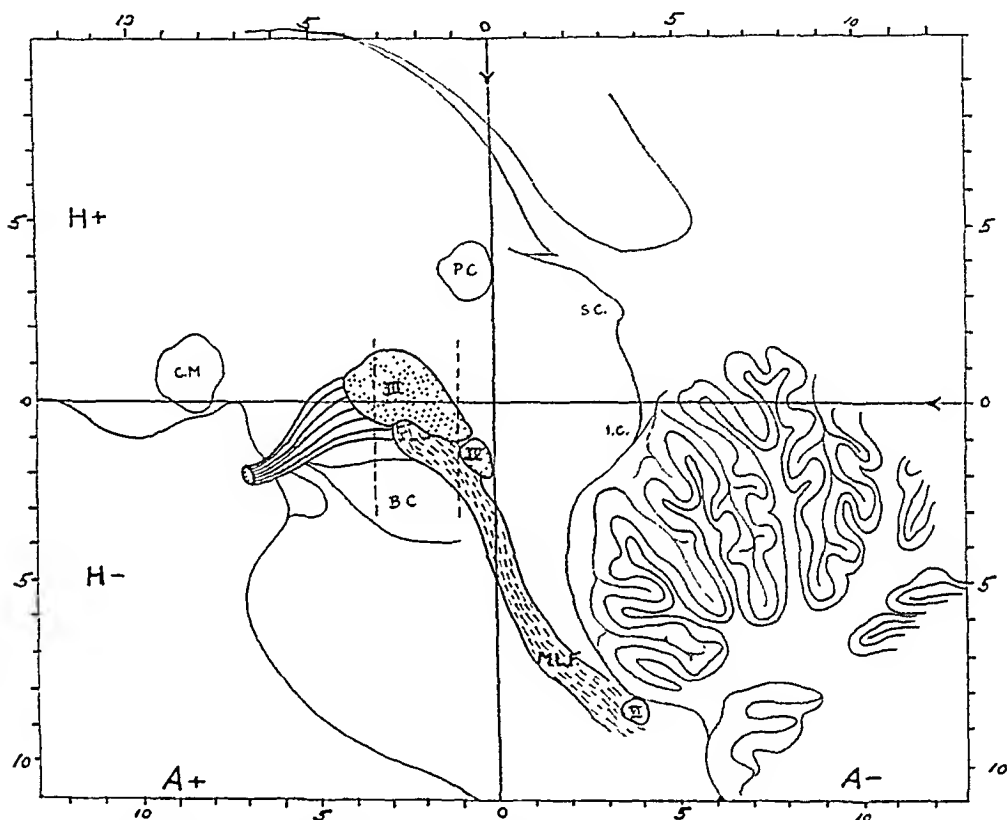


Fig. 1.—Projection drawing of a sagittal section through the brain stem of a monkey 0.5 mm. lateral to the midplane. The arrows on the zero vertical and zero horizontal lines indicate direction of stimulation. The scale on each side is expressed in millimeters. *III* indicates oculomotor nucleus and projected roots; *IV*, trochlear nucleus; *VI*, abducens nucleus; *B.C.*, brachium conjunctivum; *C.M.*, corpus mamillare; *I.C.*, inferior colliculus; *M.L.F.*, median longitudinal fasciculus; *P.C.*, posterior commissure, *S.C.*, superior colliculus; *A+* vertical planes anterior to the zero frontal plane; *A—*, vertical planes posterior to the zero frontal plane; *H+*, horizontal planes above the zero horizontal plane; *H—*, horizontal planes below the zero horizontal plane. *L* (in text) indicates planes lateral to the midsagittal plane.

From still deeper zones trochlear nucleus effects were noted, i. e. intorsion of the contralateral eye. At this point slightly greater than liminal currents yielded upward movement of the ipsilateral globe, eleva-

tion of the upper lid and intorsion of the opposite eye, a result demonstrating that the cells controlling retraction of the lid are situated in the most caudal and ventral portion of the oculomotor nucleus, adjacent to the trochlear nucleus. In this plane pupillary constriction was obtained only from the posterior commissure, never from the caudal portion of the oculomotor or the trochlear nucleus. Stimulation of the trochlear nerve roots produced ipsilateral intorsion movements.

The reactive area for ipsilateral oculomotor responses was 3 to 4 mm. in the vertical plane of the instrument, 5 to 6 mm. in the horizontal plane (fig. 1) and 0.5 to 1.5 mm. lateral to the midline. At the more

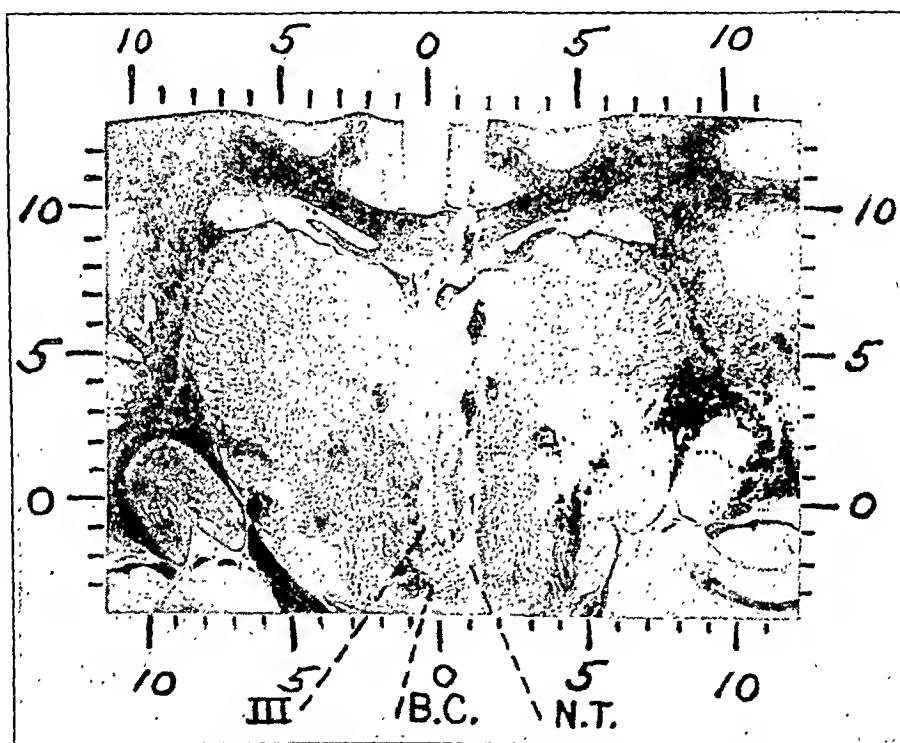


Fig. 2.—Photograph of a frontal section through the rostral portion of the oculomotor nucleus at $A + 3.2$, as indicated in the sagittal section (fig. 1). The needle tract (N.T.) is 1 mm. lateral to the midline. Abbreviations in this figure and in figure 3 are the same as those used in figure 1.

rostral and dorsal coordinates pupillary constriction and downward and inward movements of the homolateral globe were obtained (fig. 2); from the caudal and ventral region inward and upward motions of the globe and retraction of the upper eyelid were elicited (fig. 3).

Point stimulations carried out during withdrawal of the electrodes yielded the same oculomotor responses as those described when the electrodes were moved downward, but in reverse order, results which corroborated the foregoing observations. Stimulations in the horizontal

plane also confirmed the results obtained in the vertical planes. With the electrodes moving at 1 mm. intervals in a rostral direction, the following successive ipsilateral ocular movements were obtained: (1) retraction of the upper lid; (2) upward movement; (3) upward and inward movement; (4) inward movement; (5) inward and downward movement;

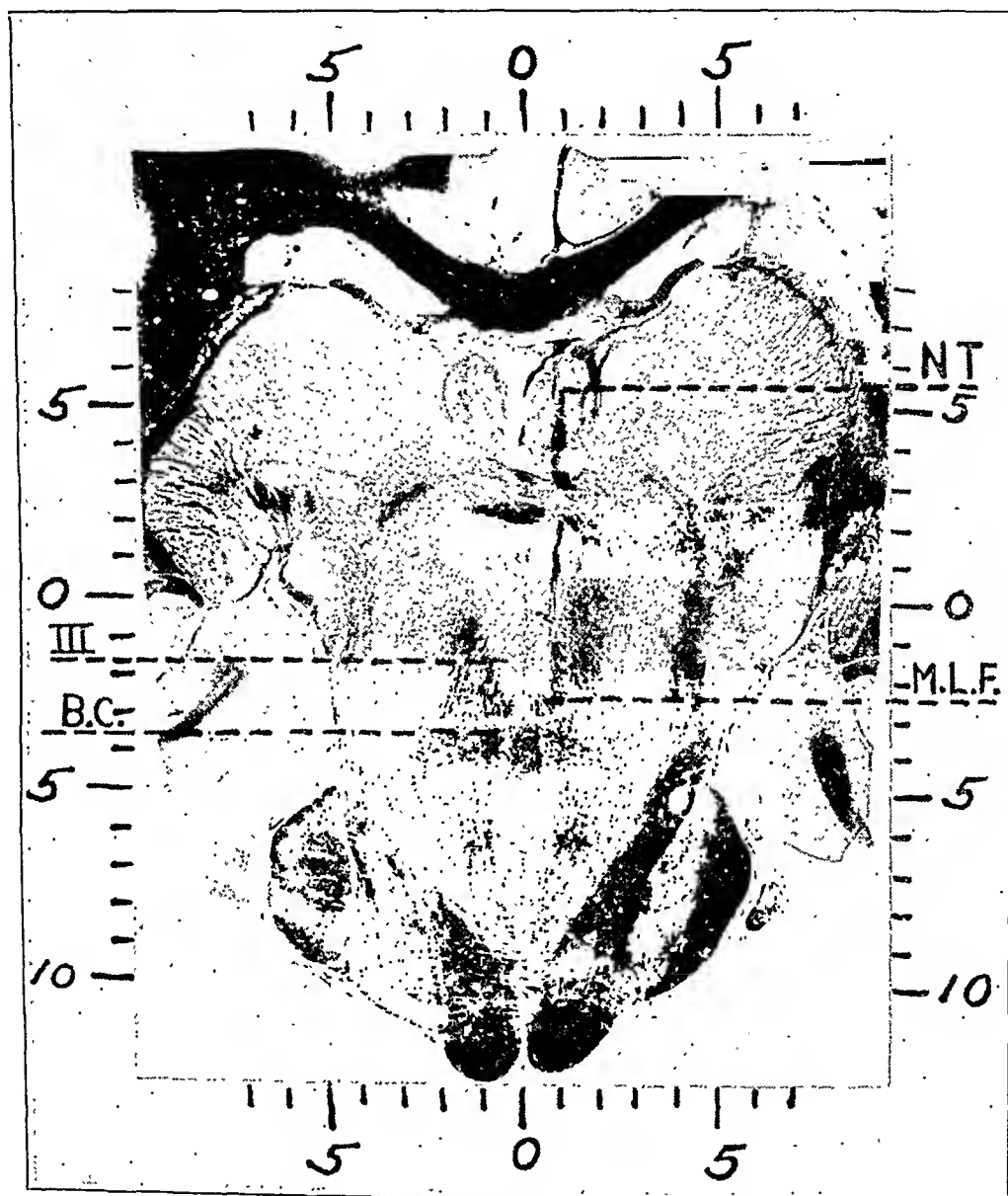


Fig. 3.—Photograph of a frontal section through the caudal portion of the oculomotor nucleus at $A + 1$ in the sagittal projection, with the needle tract running 0.4 mm. lateral to the midline.

(6) downward rotation of the globe; (7) pupillary constriction (often bilateral). A precise center for action of the inferior oblique muscle was difficult to elicit. In 4 experiments definite extorsion (action of the inferior oblique muscle) of the ipsilateral eye was observed by stimulation of the rostral zones of the oculomotor nerve roots. In 1

experiment a contralateral inferior oblique muscle effect was obtained. In order to produce extorsion movements, however, higher voltages were necessary.

Effect of Lesions.—Small electrolytic lesions were made with direct currents of 1 to 2 milliamperes directed for fifteen seconds to a focus in the dorsal and rostral region of the oculomotor nucleus. This was at a point just above that for downward movement of the globe ($A + 2.5$, $L 0.5$, $H 0$) where stimulation yielded pupillary constriction. As soon as the monkey recovered from the anesthetic, it showed on the side of the lesion (1) an enlarged pupil, which constricted slightly to light and closure of the lids and (2) defective downward movement of the globe when in the abducted position. There was no ptosis or other ocular muscle defects. The pupillary disturbance lasted over ninety-nine days, while the impairment of action of the inferior rectus muscle lasted four days.

Small electrolytic lesions were also made in the caudal and ventral region, in the "tail" of the oculomotor nucleus. This was at a point ($A + 1.0$, $L 0.7$, $H - 3.5$) where stimulations yielded ipsilateral upward and inward movement of the globe with retraction of the upper eyelid and action of the contralateral superior oblique muscle. Such a localized lesion produced partial ptosis of the superior eyelid, which lasted three days.

An electrolytic lesion in the oculomotor root fibers, converging from the nucleus toward the base of the peduncle, resulted in partial weakness of all the intrinsic and extrinsic ocular muscles supplied by the ipsilateral third cranial nerve without dissociation. This lasted many months.

COMMENT

According to our experiments, the dorsoventral and rostrocaudal arrangement of the functional representation of the ocular muscles in the oculomotor and trochlear nuclei of the monkey is as follows: (1) sphincter pupillae (usually bilateral responses); (2) inferior rectus; (3) ciliary (?); (4) inferior oblique (?); (5) internal rectus; (6) superior rectus; (7) levator palpebrarum, and (8) superior oblique (contralateral).

Except for movements of the superior oblique muscle, the actions of the extrinsic ocular muscles are purely homolateral. The functional pattern in the oculomotor nucleus which we present is considerably at variance with that which Brouwer² conjectured as existing in man. The chief corrections are in the localization of movements of the upper eyelid and the vertical rotations of the globe. On the basis of casuistic and some pathologic data from the literature and from 1 of his own cases, Brouwer² reached the conclusion that foci for the upward movement of the eyeball and superior lid were situated in the dorsal portion of

the oculomotor nucleus. The evidence which he cited, however, is hardly convincing. Bach,⁹ who made clinical, pathologic, anatomic and experimental observations on man and animals, found that centers for the upward movements of the globe and superior lid were located in the more ventral and caudal portion of the oculomotor nucleus. Von Monakow's¹⁰ clinicopathologic studies on man yielded similar conclusions. Our experimental data confirm the observations of Bach and von Monakow. At least in the monkey the centers for elevation of the globe and the upper lid are situated in the caudal and ventral portion of the oculomotor nucleus just rostral to the nucleus trochlearis. The focus for downward movement of the globe is localized to the rostral and dorsal portion of the oculomotor nucleus just ventral to the point for pupillary constriction.

The ocular movements described may be obtained in all the vertical planes running through the oculomotor nucleus, but in the order described, i. e., the most dorsal stimulations yielding downward and the most ventral upward movements. The best downward motions were observed in the rostral vertical planes. No downward rotation, however, could be elicited from the most caudal vertical planes. On the basis of these observations it would appear that the functional arrangement within the nucleus is somewhat comma shaped. In the head, or the rostral end, are situated the centers for pupillary constriction and downward movement of the globe; in the body is the focus for action of the internal rectus muscle, while in the tail, or the caudal zone, next to the trochlear nucleus, are the centers for upward movement of the globe and superior eyelid. The arrangement also seems to have a lamellar character in the horizontal plane. This lamellar distribution may be due to the arrangement in the oculomotor rootlets, which emerge from the nucleus to run in a ventral and rostral direction (fig. 3). The exact localization of the center for pupillary constriction has not been considered in detail in this investigation. This problem had already been studied in cats by Ranson and Magoun,⁷ Magoun and Ranson⁸ and Benjamin.¹¹ From our experiments it appears that the center for the sphincter pupillae in the monkey is represented in the most rostral and dorsal portion of the oculomotor nucleus, probably in the small cells of the Edinger-Westphal nucleus. An interesting observation is the bulging of the iris on stimulation of a point near the foci for pupillary constriction and action of the inferior rectus muscle. The bulge is presumably

9. Bach, L.: Zur Lehre von den Augenmuskellähmungen in den Störungen der Pupillbewegung, *Arch. f. Ophth.* **47**:339-386 and 551-630, 1939.

10. von Monakow, C.: *Gehirnpathologie*, ed. 2, Vienna, A. Hölder, 1905, p. 103.

11. Benjamin, J. W.: The Nucleus of the Oculomotor Nerve with Special Reference to Innervation of the Pupil and Fibers from the Pretectal Region, *J. Nerv. & Ment. Dis.* **89**:294-310, 1932.

due to contraction of the ciliary muscle, which, in turn, causes the lens to become more spherical and thus push the iris anteriorly.¹² That this action may be obtained without convergence or pupillary constrictor movements proves that the ciliary muscle has a distinct localization in the oculomotor nucleus.

SUMMARY

Electric stimulations and lesions were made in the oculomotor and trochlear nuclei of monkeys. These experiments indicate that individual ocular muscles are functionally represented within the ipsilateral oculomotor nucleus, while the superior oblique muscle is governed by the contralateral trochlear nucleus. The dorsoventral and rostrocaudal arrangement of functional representation of the ocular muscles is as follows: (1) sphincter pupillae; (2) inferior rectus; (3) ciliary (?); (4) inferior oblique (?); (5) internal rectus; (6) superior rectus; (7) levator palpebrarum; (8) superior oblique (contralateral).

Mr. M. Grabiner gave technical assistance.

1165 Park Avenue.

12. Hensen, V., and Völckers, C. V.: Ueber die Accommodationsbewegung der Choroidea im Auge des Menschen, des Affen und der Katze, Arch. f. Ophth. (pt. 1) **19**:156-162, 1873.

FATALITIES FOLLOWING ELECTRIC CONVULSIVE THERAPY

REPORT OF TWO CASES, WITH AUTOPSY

FRANKLIN G. EBAUGH, M.D.

CLARKE H. BARNACLE, M.D.

AND

KARL T. NEUBUERGER, M.D.

DENVER

The present widespread use of electric convulsive therapy in psychiatry prompts one to analyze carefully occasional cases of fatality from its use. Cerletti,¹ citing his original work with Bini, stated that although thousands of convulsions have been produced in patients, no deaths have occurred. In a survey of this situation by the United States Public Health Service² in October 1941, 4 such deaths were reported, which is a rate of 0.5 per thousand of the total number of patients treated by this method. As far as we have been able to ascertain, throughout the United States up to June 1942 10 deaths, including the 2 in our experience, have occurred. Of these 10 fatalities, the cause of 2 was immediate respiratory failure, the data on 1 were unknown and the electric convulsive therapy served as a contributing cause of the others. The distribution of the cases is shown in the accompanying table.

In this paper we wish to discuss 2 cases of death of patients receiving electric convulsive therapy.

REPORT OF CASES

CASE 1.—A man aged 57 with a depressive psychosis was given electric shock therapy, with the induction of twelve grand mal and one petit mal seizure. A careful preliminary preshock series of investigations was made, including routine examination by a cardiologist, who reported that the heart was organically intact

From the University of Colorado School of Medicine and the Colorado Psychopathic Hospital.

Read at the Sixty-Seventh Annual Meeting of the American Neurological Association, Chicago, June 4, 1942.

1. Cerletti, U.: Annotazioni sull' elettroshock, *Wien. med. Wchnschr.* **90**: 1003, 1940.

2. Kolb, L., and Vogel, V. H.: The Use of Shock Therapy in Three Hundred and Five Mental Hospitals, *Am. J. Psychiat.* **99**:90 (July) 1942.

Age, Yr.	Number of Electric Shock Treatments Given	Diagnosis	Date and Cause of Death	Autopsy Observations
State Hospital Group				
45	62 (over a period of 5½ months, to July 1941)	Schizophrenic reaction	August 1941; cardiac failure	To be reported in literature
29	19 "electric stimulating treatments," without single grand mal reaction; previous insulin treatment	Manic-depressive psychosis, with several previous attacks	Status epilepticus 3 days after last treatment; medical examiner made diagnosis "coronary thrombosis and influenza" on death certificate	Autopsy not permitted
56	22 brief subconvulsive treatments and 30 convulsive treatments	Manic-depressive psychosis, mixed type	3 months after treatment, as result of acute respiratory infection and septicemia	Permission for autopsy not obtained
75	3 electric shock treatments with curare, with improvement	Manic-depressive psychosis, depressed type; advanced generalized arteriosclerosis	After third treatment cardiac fibrillation, probably ventricular, with immediate death	Advanced cerebral arteriosclerosis; chronic leptomenigitis; atherosclerosis of aorta; acute passive congestion of the lungs, liver and spleen
Private Hospital Group				
79	6 electric shock treatments	Manic-depressive psychosis, fifth attack; patient discharged as improved; later operation for cataract, with return of symptoms	4 months after last electric shock treatment, with cardiac failure	Reports not available at present
58	1 treatment	Schizophrenic reaction	Death after first treatment "due to involvement of central nervous system and preceded by respiratory failure"	Permission for autopsy not obtained
?	Data not obtainable			
50	1 treatment	Manic-depressive reaction	After grand mal seizure; patient never regained consciousness	Reports not available at present
Cases Reported in This Paper				
57	13 electric shock treatments given, with 12 grand mal and 1 petit mal seizure	Agitated depression	April 3, 1941, 1 hr. 35 min. after grand mal reaction; coronary thrombosis	Coronary occlusion and myocardial infarction; small areas of cortical devastation; diffuse degeneration of cortical nerve cell; astrocytic proliferation
57	3 treatments, with 2 petit mal and a terminal grand mal seizure	Manic-depressive psychosis, manic type	Jan. 11, 1942, following third shock and first grand mal seizure with immediate respiratory failure	Small areas of recent necrosis in cortex, hippocampus and medulla; astrocytic proliferation

and that the electrocardiogram revealed nothing abnormal. The average dose of electrical current was 85 volts and 900 milliamperes administered for a duration of fifteen-hundredths second. The treatments were given biweekly. After the last grand mal convulsion the patient complained of pain suggesting angina pectoris and died within one and one-half hours.

Autopsy Observations.—The main pathologic changes were observed in the heart and brain. The heart was slightly hypertrophied and showed a soft, moist, discolored area in the upper half of the anterior wall and interventricular septum. The horizontal branch of the left coronary artery was firm and thickened and showed several elevated and partly calcified plaques. The descending branch was converted into a rigid, calcified tube with many narrowing plaques. Its

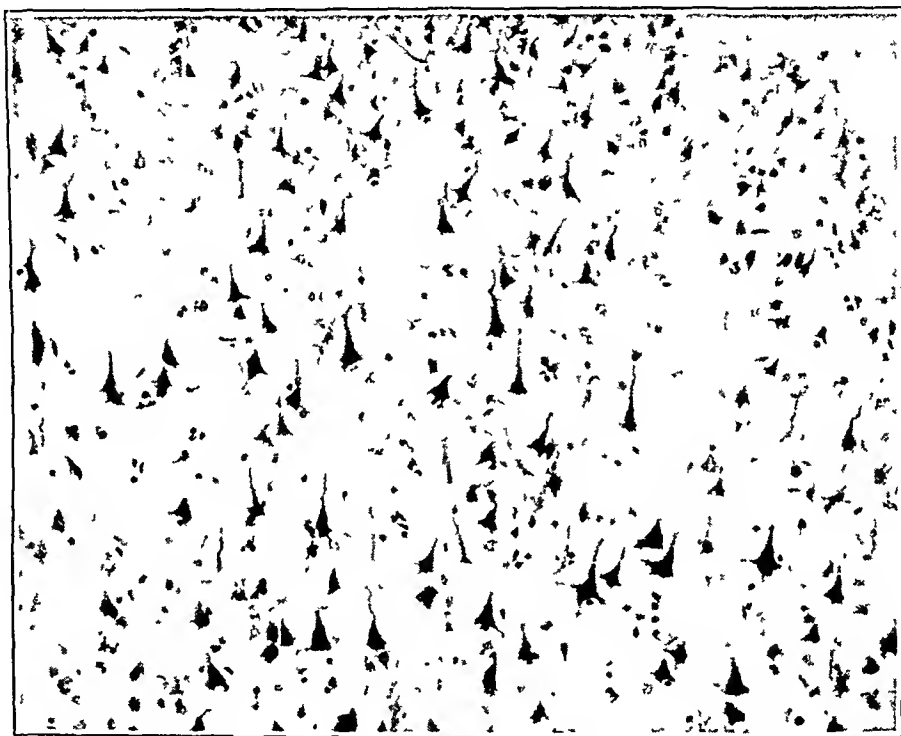


Fig. 1 (case 1).—Irregular cortical architecture; sclerosed nerve cells; ghost cells. Nissl stain.

upper part was impervious for a distance of about 4 cm.; the lumen was occluded by adherent brownish thrombotic masses, which had been deposited on the surface of coalescing ulcerated plaques.

The brain appeared normal in shape, size and weight. The arteries were thin walled and free from sclerosis. Sections through the brain revealed only one isolated petechia, lying in the subcortical white matter of the left occipital lobe.

Microscopic Study.—Sections taken from the myocardium showed a number of small, old cellular scars in various portions. The area displaying grossly the diminished firmness exhibited several spots of poor stainability and splitting and tortuosity of muscle fibers; nuclei were in part unstainable, while others appeared dark and shrunken.

Blocks taken from various areas of the brain were examined histologically by numerous methods.³ Under low magnification the brain tissue appeared fairly normal at first sight, but closer examination revealed a number of changes,

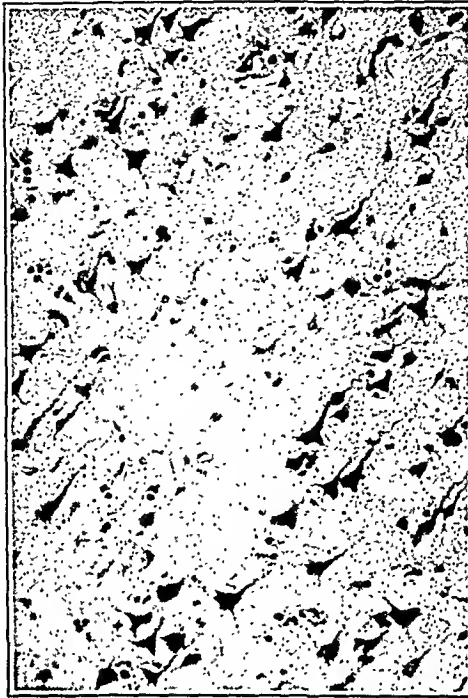


Fig. 2 (case 1).—Circumscribed area of recent cortical necrosis. Nissl stain.

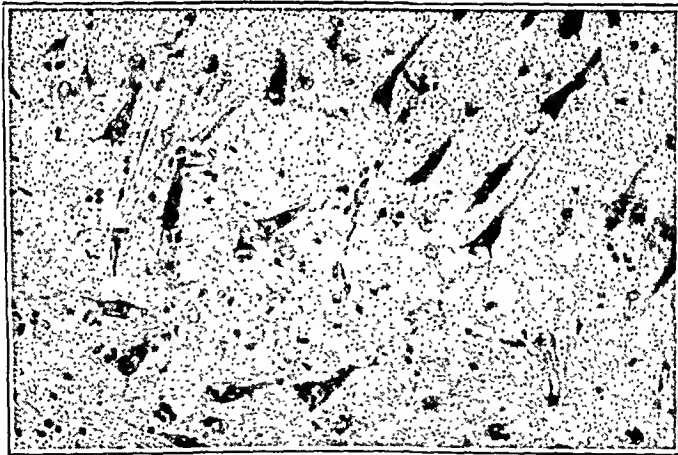


Fig. 3 (case 1).—Astrocytic proliferation in the hippocampus. Nissl stain.

3. In both cases frontal, parietal, temporal and occipital regions of the cortex, the interbrain, the basal ganglia, the thalamus, the substantia nigra, the pons, the cerebellum and the medulla were examined; the staining methods of Nissl, Penfield, Bielschowsky, Holzer, Rio Hortega, Cajal and Loyez were applied, in addition to the use of hematoxylin and eosin and stains for fat.

predominantly located in the frontal and temporal lobes. Several small areas of devastation appeared to be entirely devoid of nerve cells or contained some ghost cells. In some of these areas the glia showed a certain activity; there were a few swollen astrocytes and *Gliarosen*; in addition, a limited number of proliferated microglia cells were occasionally observed, their processes containing tiny granules of fat in some instances. Furthermore, there was diffuse degeneration of nerve cells in the cortex, which was most pronounced in the tops of the convolutions. This degeneration consisted chiefly in shrinkage or sclerosis of cells, which appeared dark and elongated with tortuous dendrites. Occasionally there was slight vacuolation of the cytoplasm. Elsewhere, paleness or ischemic degeneration of scattered nerve cells was seen, the neurons being faintly stained, slender and triangular, with pale, triangular nuclei. Owing to these lesions, the architecture of the cortex appeared irregular in places. The number of astrocytes was diffusely increased in a slight to moderate degree in the upper and deep cortical layers. The hippocampus showed ischemic changes in scattered nerve cells and small areas with swollen astrocytes and absence of nerve cells. There was also an increase in the number of astrocytes in the polymorphic cell layer of the hippocampus. Other regions of the brain showed the changes described to a far less degree. The senile lipid pigment in the neurons was perhaps more prominent than normal for the age of the patient. Senile plaques and fibrillary alteration were not seen. No demyelination was noted. Arteries and arterioles were practically free from sclerosis. Small accumulations of perivascular pigment were occasionally seen in the white matter. There was no noteworthy damage to the neurofibrils.

CASE 2.—A man aged 57 was treated by electric shock for a manic reaction. He died after the third treatment, immediately after the first grand mal seizure. Treatments were given at weekly intervals, and during the first two petit mal attacks the patient experienced respiratory difficulties after the seizure. It was thought that these reactions were due to administration of curare. Oxygen was administered, as well as prostigmine methylsulfate. In the last treatment the grand mal convulsion was produced with 85 volts and 900 milliamperes, given for fifteen-hundredths second. Respiration immediately ceased and, despite artificial respiration, administration of the usual stimulants and heroic measures, was never reestablished.

Autopsy Observation.—No satisfactory explanation of the sudden death was obtained.

Microscopic Study.—Examination of the organs of the body was noncontributory. Microscopic changes in the brain were present throughout the cortex and were not notably accentuated in the frontoparietal region, through which the electric current is supposed to have passed. The cortical architecture was fairly well preserved. However, there were areas within which a number of nerve cells were pale or showed frank ischemic change. This as a rule was so pronounced as to be recognizable under low magnification. No area with loss of all the nerve cells was seen. Scattered single nerve cells throughout the cortex had undergone similar changes. A few nerve cells in Sommer's sector of the hippocampus showed early ischemic change.

Glial reactions were slight. However, occasional small rod cells were visible in involved areas, and swelling of the astrocytes was discernible. Glial changes were more noticeable in the hippocampus, particularly in the polymorphic layer. In this region the nerve cells appeared to be fairly well preserved but were

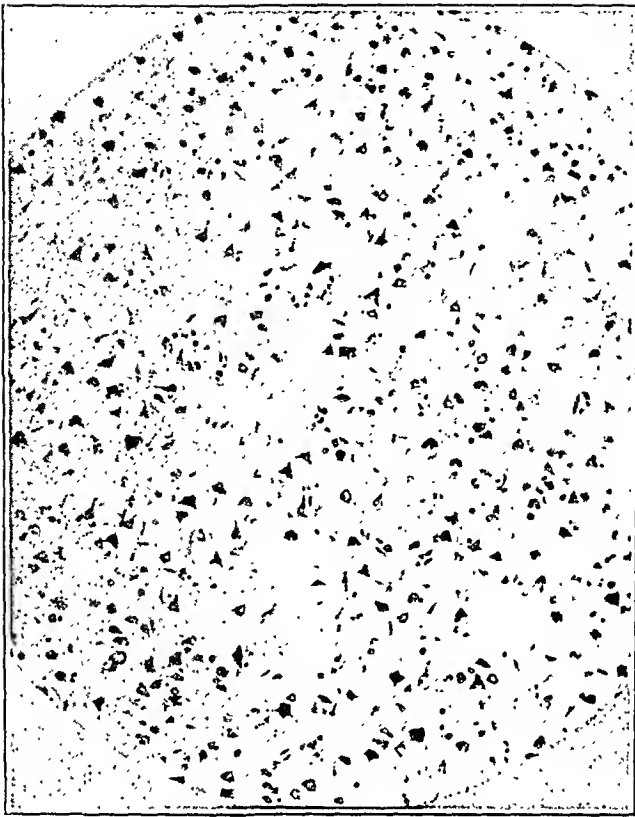


Fig. 4 (case 2).—Irregular cortical architecture; dropping out of neurons; rod cells. Nissl stain.

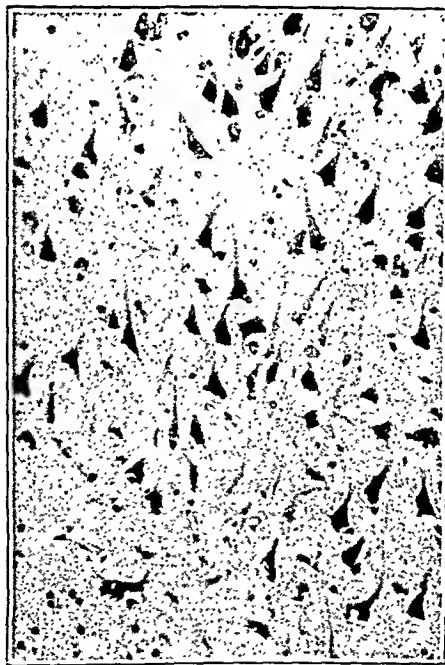


Fig. 5 (case 2).—Recent ischemic changes in nerve cells of the hippocampus. Nissl stain.

somewhat reduced in number, a few degenerating neurons being seen. Many astrocytes, with pale, enlarged nuclei and swollen cytoplasm, were visible with the Nissl stain. In Cajal stains their number was estimated to be at least twice the normal.

In the thalamus occasional nerve cells showed very pale, poorly defined and vacuolated cytoplasm, with somewhat distorted nuclei and in some instances breaking up of the nucleoli. Occasional swollen astrocytes were seen, and small glia nodules as well; neuronophagia was noted in rare instances.

In the basal ganglia the large cells of the striatum were in fair to good condition. The small cells showed occasional satellitosis and changes similar to

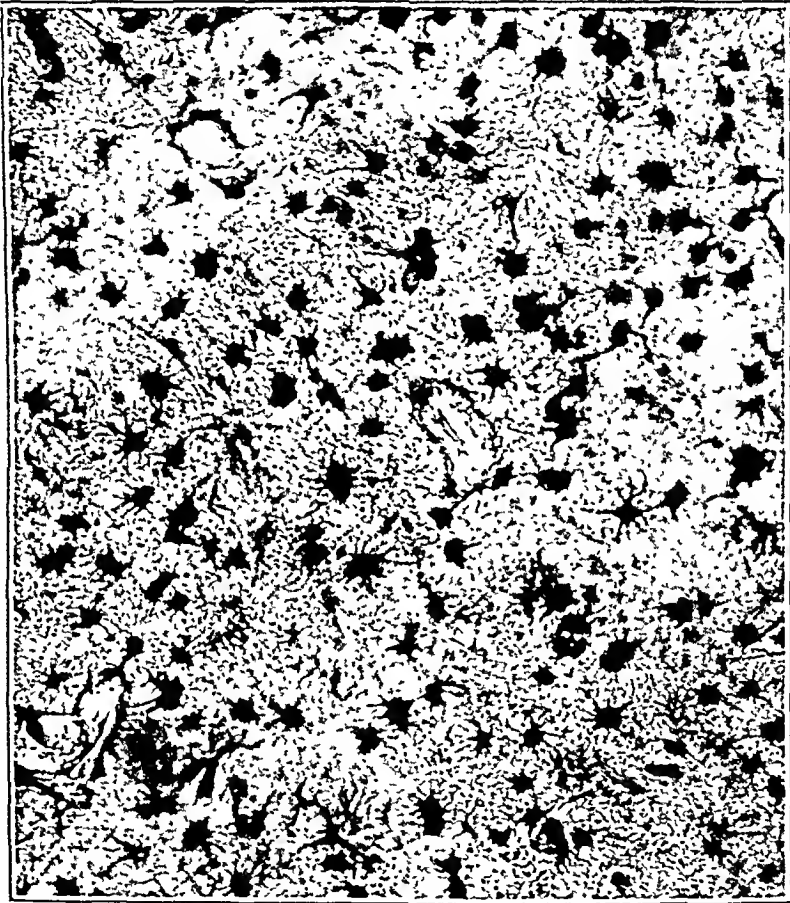


Fig. 6 (case 2).—Astrocytic proliferation in the hippocampus. Cajal stain.

those in the thalamus. A few ghost cells and some swelling of astrocytes were observed. The changes had a patchy distribution, with areas in the very vicinity which appeared normal. The globus pallidus was in good condition, with occasional traces of swelling of the vascular endothelium and very slight round cell infiltration about a small number of veins.

The medulla was normal in most areas. However, the dorsal vagus nucleus, particularly on the left, showed occasional pale cells with satellitosis and ghost cells with neuronophagia. Enlarged glial nuclei and small *Gliarsen* were seen in places. Similar, but less pronounced, glial activity was observed in the substantia reticularis and in the nucleus arcuatus.

All other areas examined were practically normal except for slight, almost negligible, changes of the types already described.

COMMENT

The death in the first case was undoubtedly due to the severe coronary disease with resulting very early infarction of the myocardium, superimposed on older myocardial damage. Death would probably have occurred at any rate within a short time, independent of the electric shock therapy. However, the treatment may have accelerated the death. It may well be assumed that the collateral circulation and the blood supply of the heart were sufficient while the patient remained quietly in bed; the electric shock probably was an increased burden on the heart, leading to failure of coronary blood supply. It is known that electric shock of any kind may involve the coronary circulation, and may even cause symptoms of angina pectoris (Alexander⁴ and Huellstrung⁵). While in the case of a patient with a normal heart this would not come into question on application of the customary electric shock treatment, with its weak current, it is easily understood that a patient with severe sclerosis of the coronary arteries would not be able to endure the shock.

The explanation of the fatal outcome in the second case meets with great difficulties. The changes in the brain cannot be considered directly responsible for the death. They are indicative of some damage suffered by the brain during the shock treatment, but they do not answer satisfactorily the question of the cause of death.

It has been known for a considerable time that different persons react differently to electric trauma. The literature furnishes examples of persons having been killed by currents of 46 volts and 1/100 ampere (Welz⁶). Thus, one might assume an individually increased susceptibility to slight electric trauma.

Furthermore, it must not be forgotten that the grand mal seizure may lead to apnea, "since it produces oxygen lack which depresses the respiratory center, and it also leaves the patient in a comatose state, with a variable degree of airway obstruction due to spasm or collapse of the pharynx, larynx, lips and tongue," as asserted by Brill and Kalinowsky.⁷ These authors stated recently that no fatal accident has yet been reported and that the only danger of the electric shock therapy lies in the possibility of postconvulsive respiratory arrest; they reported a case of serious but nonfatal asphyxia following a grand mal attack during electric shock treatment.

4. Alexander, L.: Neuropathological Aspects of Electric Injuries, *J. Indust. Hyg. & Toxicol.* **20**:191, 1939.

5. Huellstrung, P.: Starkstromunfall als Ursache von Angina pectoris, *Klin. Wchnschr.* **13**:409, 1934.

6. Welz, A.: Starkstromtod und Hirntod, *Virchows Arch. f. path. Anat.* **305**: 646, 1940.

7. Brill, H., and Kalinowsky, L.: Asphyxial Episodes and Their Prevention in Electric and Other Convulsive Therapies, *Psychiatric Quart.* **16**:351, 1942.

We may well assume that the course of events was similar in the present case, with its sudden onset of respiratory failure after the attack. Wortis and his associates⁸ have recently stated that electrically produced convulsions inhibit oxygen uptake, a statement which also agrees with our explanation.

Our assumption appears all the more justified in that lesions in the medulla were observed. It must be admitted that they were slight and per se probably without great significance. They do show, however, that the medullary centers reacted in an unusual fashion to the electric shocks. (Even after his two petit mal seizures the patient had respiratory trouble.⁹) These centers may have failed, accordingly, in the grand mal seizure provoked by the last electric shock.

The histologic changes in the brain are interesting from several points of view. As not only in the first case but also in the second glial reactions were exhibited which must be considered older than a few minutes, we are entitled to assume that not the grand mal seizure but the action of the electric current on the brain produces such glial changes, unless the petit mal seizure is the cause, which is unlikely. Histologically, well discernible lesions in the neurons may develop experimentally within a few minutes (Heilbrunn and Liebert¹⁰), but according to all experiences proliferative changes in the glia require more time. While, therefore, the changes in the nerve cells may in part be a sequel of the last grand mal seizure, the glial reactions are certainly older and must have been produced by the former shocks, which were followed only by petit mal seizures.¹¹ Corresponding conclusions must be drawn regarding the first case. Here, however, the great number of grand mal seizures over a long time renders statements as to the genesis of the histologic lesions more difficult. All the lesions observed in the brain in both cases were brought about by the electric shock treatment, partly, in our opinion, in connection with the seizures produced by that treatment; neither the mental condition nor the pathologic changes elsewhere in the body can be made responsible for these lesions.

The histologic lesions in the brain are not to be considered serious. Certainly, many of the changes were reversible. The bulk of the parenchyma was left intact. The changes described were in no instance incompatible with longer duration of life, and they were by no means

8. Wortis, S. B.; Shaskan, D.; Impastato, D., and Almansi, R.: The Effects of Electric Shock and Some Nerve Drugs, *Am. J. Psychiat.* **98**:354, 1941.

9. The role played by curare appears doubtful.

10. Heilbrunn, G., and Liebert, E.: Biopsies of the Brain Following Artificially Produced Convulsions, *Arch. Neurol. & Psychiat.* **46**:548 (Sept.) 1941.

11. The question whether one epileptic seizure may produce histologically discernible changes in nerve cells in the human brain cannot be definitely answered and will not be discussed in this paper.

likely to interfere seriously with the normal function of the central nervous system. One would not be justified in suggesting rejection of electric shock therapy on account of the fatalities reported; these fatalities should only arouse doubts as to its applicability in the treatment of elderly patients, particularly if there is evidence of cardiac involvement.

In each of the 2 cases reported a cardiologist was called in consultation, complete collaborative electrocardiograms were made and on the basis of negative evidence treatment was approved. The indications and contraindications for this type of drastic therapy must always be carefully evaluated. We should advise repeated check-ups by the cardiologist during the progress of the treatment.

The stimulation of the astrocytes in both cases was considerable and recalls what Weil and Liebert¹² described in their neuropathologic study of cases of psychoses in which metrazol was used.

The changes were not limited to the pathway of the electric current, although it must be admitted that they were perhaps slightly more marked in this region, particularly in the first case; the differences, however, were so little pronounced as to be almost negligible.

The cerebral lesions are probably due both to direct action of the current on the parenchyma (diffuse lesions) and to circulatory disturbances brought about by the current (focal lesions) in wide areas of the brain (Morrison, Weeks and Cobb¹³; Alexander¹⁴; Echlin¹⁵). The cerebral damage in our case was not much different from that seen in animal experiments (Neubuerger, Whitehead, Rutledge and Ebaugh¹⁶).

Different species of animals seem to react in a different fashion to electric shock. While we saw parenchymal changes of a slight degree as a predominant feature in dogs, Alpers and Hughes¹⁷ observed hemorrhages in the brain and meninges in cats.

12. Weil, A., and Liebert, E.: Neuropathologic Study of Six Cases of Psychoses in Which Metrazol Was Used, *Arch. Neurol. & Psychiat.* **44**:1031 (Nov.) 1940.

13. Morrison, R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock in Mammalian Brains, *J. Indust. Hyg. & Toxicol.* **12**: 324, 1930.

14. Alexander, L.: Electric Injuries of the Nervous System, *Arch. Neurol. & Psychiat.* **47**:179 (Jan.) 1942.

15. Echlin, F. A.: Vasospasm and Focal Cerebral Ischemia: Experimental Study, *Arch. Neurol. & Psychiat.* **47**:77 (Jan.) 1942.

16. Neubuerger, K. T.; Whitehead, R. W.; Rutledge, E. K., and Ebaugh, F. G.: Pathologic Changes in the Brains of Dogs Given Repeated Electrical Shocks, *Am. J. M. Sc.* **204**:381 (Sept.) 1942.

17. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, *Arch. Neurol. & Psychiat.* **47**:385 (March) 1942.

SUMMARY

Two fatalities following electric shock treatment are reported. In the first case death was due to coronary occlusion and myocardial infarction. In the second case the general autopsy observations were without significance. It was assumed that the fatal outcome was due to post-convulsive respiratory arrest. Both cases showed rather widespread, but not serious, histologic changes in the brain. The pathogenesis and the significance of the histologic changes are discussed. The importance of repeated careful investigations of cardiac function in patients who are considered for electric shock treatment is emphasized.¹⁸

University of Colorado School of Medicine and Hospitals.
4200 East Ninth Avenue.

18. The articles by B. J. Alpers and J. Hughes (The Brain Changes in Electrically Induced Convulsions in the Human, *J. Neuropath.* **1**:173-180, 1942) and by G. Heilbrunn and A. Weil (Pathologic Changes in the Central Nervous System in Experimental Electric Shock, *Arch. Neurol. & Psychiat.* **47**:918-930 [June] 1942) had not come to our attention when this paper was completed.

ACUTE SYPHILITIC ANTERIOR POLIOMYELOPATHIC SYNDROME

REPORT OF A CASE

LEWELLYS F. BARKER, M.D.

BALTIMORE

In rare instances syphilis has been reported as responsible for the origin of the syndrome of acute anterior poliomyelitis. Another case is here added to the list.

REPORT OF CASE

A white man aged 29 was admitted to the Johns Hopkins Hospital (service of Dr. W. T. Longcope) on March 22, 1942, complaining of inability to swallow and weakness of both legs. The illness began a fortnight earlier with sore throat and temporary double vision. Later he had difficulty in swallowing (fluids regurgitating through the nose) and increasing paralysis of the legs. A lumbar puncture (done at another hospital on the day before admission) revealed a cell count of 100 cells (small mononuclears) per hundred cubic centimeters of fluid and an increase of globulin. It was believed that he had acute anterior poliomyelitis, and he was sent to the isolation ward of the Johns Hopkins Hospital.

His earlier history was without significance except for gonorrhea at the age of 29. He denied having had other venereal infections. He was married and had 2 healthy children.

Physical examination revealed pronounced dysphagia, flaccid paralysis of both lower extremities, moderate weakness of the muscles of the upper extremities and absence of knee and ankle jerks. The pupillary reactions, the sphincters and the superficial reflexes were at that time normal.

Laboratory tests revealed slight leukocytosis (10,700 cells) and strongly positive Wassermann reactions of the blood and cerebrospinal fluid.

Though an orthopedic consultant favored the diagnosis of acute anterior poliomyelitis, the internists thought it probable, in view of the serologic reactions, that syphilis was responsible for the whole clinical picture, especially as the age of the patient, the season of the year, the insidious onset of the illness, the absence of pain and the peculiar distribution of the paralyses were out of accord with the diagnosis of ordinary poliomyelitis.

Five days after admission, the patient became unable to void urine and had to be catheterized regularly. Slight hypesthesia of the left thigh developed. The disturbance of bladder function, as well as the hypesthesia, favored the diagnosis of neurosyphilis rather than that of Heine-Medin disease. Moreover, absence of the virus of poliomyelitis from the feces was proved by inoculation of monkeys by Dr. H. A. Howe.

Under intensive antisyphilitic therapy (bismosol, potassium iodide and intravenous injections of mapharsen) rapid improvement occurred. By March 29 the patient could swallow, and tube feeding was discontinued. Muscular strength increased later, and the cell count of the spinal fluid fell to 6 cells per cubic millimeter. By May 23 the symptoms had largely disappeared. Though there

was still some weakness of the lower extremities, it seemed probable that further antisyphilitic treatment would make the cure complete.

It seems certain that in this case one was dealing with meningo-vascular syphilis with vascular narrowing (or occlusion) in the domain of the system of the sulcocommissural arteries distal to the branches that supply the commissure, Clarke's columns and the bases of the posterior horns. In this connection the diagram of the arterial supply of the spinal cord accompanying Stähli's article is worthy of careful study. When more proximal arteries are thrombosed, complete recovery can scarcely be expected.

When an acute anterior poliomyelopathic syndrome appears in a patient who has syphilis, it would seem wise, therefore, to institute intensive antisyphilitic treatment promptly on the chance that changes in the cord that are not already irreparable may be prevented from becoming so by restitution of better circulatory conditions in the cord through regression of the vascular syphilitic process.

1035 North Calvert Street.

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ARTERIAL HYPERTENSION FOLLOWING METRAZOL SHOCK THERAPY

WILLIAM C. MENNINGER, M.D.

TOPEKA, KAN.

Shock therapy has become one of the most widely used treatments in psychiatric practice. No report could be found in the literature of the initiation of hypertension following the use of metrazol shock therapy. In the following case hypertension developed during a course of metrazol shock treatments and has persisted over the four years since the treatment.

REPORT OF A CASE

A woman aged 47, with a negative family history for hypertension, had married when 26 years of age and had given birth to two children, now aged 18 and 15, who are healthy. She had a "nervous breakdown" at the age of 28, from which she recovered without hospitalization, and made a satisfactory and happy adjustment until her present illness. Her husband's death in 1934 was a severe blow to her. Because of metrorrhagia artificial menopause was produced by roentgen therapy in January 1936. After this she appeared less well physically to her friends and family, but made no specific complaints. In November 1936 she manifested her first mental symptoms, in the form of somatic delusions. She became depressed and self depreciatory and expressed the belief that her heart had stopped beating and that her organs had disintegrated. She was admitted to a general hospital just before Christmas 1936, but showed no improvement; she was transferred to the Menninger Psychiatric Hospital in June 1937.

Here she failed to respond to milieu therapy but continued to have delusions and at times required tube feeding. After hearing reports of beneficial results with metrazol shock therapy for depressions (my associates and I first used it for schizophrenia in October 1937), we decided to employ it in this case. The original physical examination had revealed only that the patient had had a previous amputation of the breast (in 1935) and was 20 pounds (9.1 Kg.) underweight. The results of laboratory examination were normal. The blood pressure, measured repeatedly over several months, ranged from 100 to 122 mm. systolic and 74 to 88 mm. diastolic.

The first metrazol treatment was given on May 3, 1938; the blood pressure before the treatment was 110 systolic and 80 diastolic, and five minutes after the treatment it was 130 systolic and 90 diastolic. In the second treatment, on May 10, the pretreatment pressure was 120 systolic and 80 diastolic and the post-treatment pressure was 150 systolic and 100 diastolic. On the fourth treatment, on May 17, the pretreatment pressure was 160 systolic and 110 diastolic, and the post-treatment pressure was 180 systolic and 100 diastolic. On the fifth treatment, on May 24, the initial pressure was 140 systolic and 100 diastolic and the pressure after the treatment was 170 systolic and 100 diastolic. On the seventh treatment,

From the Menninger Psychiatric Hospital.

on May 27, the initial pressure was 164 systolic and 100 diastolic and the post-treatment pressure was 200 systolic and 110 diastolic. Because it was observed that the blood pressure remained elevated and the seven treatments had produced no improvement in the mental picture, the metrazol therapy was stopped.

The shock therapy did not change the patient's mental state. She dreaded each treatment and on every occasion manifested great anxiety prior to the session. However, she responded some twelve months later to psychotherapeutic help, which, however, was not attempted systematically until about six months after the metrazol therapy. She improved sufficiently to leave the hospital in February 1941 (three and a half years after admission), and since that time she has reestablished her home, social and community activities and has been fairly well, both physically and mentally. The significant change following the metrazol therapy was the increased blood pressure, which has remained consistently between 175 and 190 systolic and 115 and 125 diastolic. There has been no physical complaint, and physical and laboratory studies have revealed nothing abnormal.

COMMENT

Although a careful search has been made of the literature, the complication or association of hypertension with metrazol therapy apparently has not been recorded. It is well recognized that the blood pressure usually increases at the time of the convulsion, just as it did in this case, and that the anxiety manifested prior to the treatment often gives rise to considerable increase in blood pressure. A survey of 100 cases in which we employed treatment with metrazol similar to that in this case (before we began the use of curare and electroshock therapy) showed the following figures for maximum blood pressure occurring during the course of a series of treatments:

Mm. Systolic	No. of Cases
No rise over 140.....	17
140 to 149.....	6
150 to 159.....	15
160 to 169.....	13
170 to 179.....	8
180 to 189.....	17
190 to 199.....	6
200 to 209.....	5
Over 210 (the highest 220).....	3
Fall from pretreatment to post-treatment pressure.....	10

In the last group of cases those in which there was a fall from the pretreatment to the post-treatment pressure, the decrease is probably explained on the basis of the anxiety and apprehension manifested in anticipation of the treatment.

The mechanism of the cardiovascular dynamics or the psychodynamics in this case is not clear. One might speculate that the anxiety and fear connected with the treatments were as important in producing

the hypertension as was the drug or the convulsions. The clinical psychiatric picture did not change at the time, either as a result of the treatments or with the development of the hypertension, but later it did. The psychologic state, as shown by the delusions both before and after the metrazol treatment, was nihilistic: The patient said that she had no stomach, no lungs, only "what remained of a brain," etc. She pleaded to "be done away with" though she never made any suicidal attempts. The unconscious psychologic state, as represented by her hypertension, remains self destructive, even to the present time. Many psychotherapeutic sessions, continued up to the present, have disclosed a continued technic of self defeatism, great activity and effort, with at times poor efficiency, and many dreams in which through some action on her own part she is acutely threatened. Even without an explanation of the cause of the hypertension, this case seemed of sufficient importance to be reported.

Menninger Psychiatric Clinic.

Technical and Occasional Notes

AN APPARATUS TO BE USED IN RECORDING TREMORS

ARTHUR ALLEN MORRIS JR., B.A., DURHAM, N. C.

In the present report an efficient and flexible method for recording tremor is described. Numerous ways of obtaining graphs with a Marey tambour, or related apparatus, have been devised, of which that used by de Jong¹ is one of the most recent and best.

The method reported here utilizes a rubber diaphragm over the rim of an ordinary "balanced armature" loud speaker. The cone has been sealed with multiple layers of collodion and the rubber diaphragm cemented with rubber cement to assure air tightness within the chamber. With the tremulous hand placed on the diaphragm, motion is transmitted mechanically and produces variation in the reluctance of the magnetic path, which thus sets up in the alternating current coils a varying electromotive force. This, in turn, is amplified and recorded by the electromagnetically operated ink-writing pens of a Grass electroencephalograph.² The paper can be run at different speeds, 3 cm. per second being the rate most often used in this clinic.

This particular unit is designed to vibrate the movable aluminum button in the throat of the cone. A short soft iron bar, armature or reed is pivoted at its center, so that its ends are free to swing back and forth like a seesaw about this pivot. Each end of the armature moves between two pole pieces of the permanent polarizing magnet, and these are arranged with the relative magnetic polarity shown in figure 1. Around the armature is a stationary coil consisting of several thousand turns of fine wire, through which the current is sent. Enough clearance is provided between the armature and the inside of the coil so the motion of the armature is not restricted by the coils.

The balanced armature unit has a high degree of perfection and will give good performance if it is operated properly, with some regard for its limitations. One of its serious limitations is that for good sensitivity the air gap between the armature and the pole pieces must be made very small in order to reduce the reluctance of the magnetic circuit and to obtain a strong magnetic field. If the air gap is made large in order to provide for greater amplitude of vibration, the strength of the field decreases, with a proportionate loss in sensitivity. However, this presents no

From the Departments of Neuropsychiatry and Physiology, Duke University School of Medicine.

1. de Jong, H., and Schaltenbrand, G.: *Deutsche Ztschr. f. Nervenhe.* 86:129, 1925; *Neurotherapie* 7:1, 1925. These investigators described the use of an ordinary muscle pelote attached to the recording muscle by a wide leather band. A tube with a fitting piece connected the pelote to a Marey tambour. The lever of the tambour was so arranged as barely to touch the surface of the smoked drum.

2. The amplifiers were built by Mr. A. M. Grass, 100 North Bayfield Road, Quincy, Mass.

serious problem, for the frequency of the Grass electroencephalograph is limited to approximately 75 to 100 per second.

The mechanism of action is shown in figure 1, and samples of records obtained from patients are given in figure 2 *A* and *B*.

APPLICATION OF APPARATUS

This apparatus is most valuable in recording fine tremors. The Grass apparatus is easily capable of measuring a frequency of 75 per

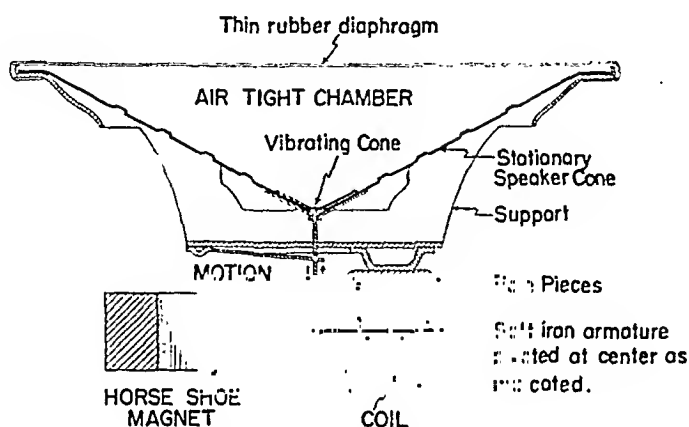


Fig. 1.—Cross section of the unit.

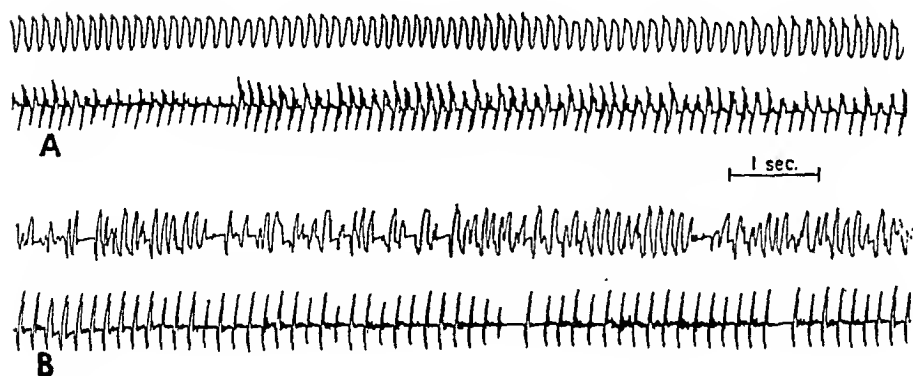


Fig. 2.—*A*, recordings of the tremor in a case of paralysis agitans (top) and the diadokokinesis (tapping) of the same hand (below). Note the regular, 7 to 8 per second tremor, with tapping at 7 to 8 per second.

B, recordings, showing the hysterical tremor of the hand (top) and the diadokokinesis of the same hand. Compare with *A*. Note the grossly irregular tremor, with several runs of waves at 8 to 10 per second, and the tapping, which is distinctly slower than the faster rates of tremor.

second, which is at least three times as fast as is necessary in clinical work. It is a simple matter to attenuate the excursion of the recording needles to differentiate tremor from variations in the position of the hand and fingers.

The apparatus is particularly valuable in measuring the irregularities in the total picture, including waxing and waning of the tremor, both fine and coarse.

The apparatus is flexible, for it can be used in any plane. Horizontal tremors of the hand are especially easy to evaluate, both as to frequency and as to irregularity in form of the oscillations, as well as to disappearance of tremor under various situations. The apparatus is small enough to hold in the hands, if desired, which permits the examiner to adapt to unusual positions or even to follow slowly moving parts, such as the head in cases of torticollis.

The apparatus is simple to use with the electroencephalographic apparatus. It does not cause outside static electricity sufficient to interfere with the simultaneous recording of electromyograms.

It has three limitations: (1) Coarse, irregular movements, such as those of athetosis or chorea, cannot be evaluated; (2) there can be no differentiation of asymmetric finger movements which bring different fingers down successively in a series of contacts with the diaphragm, unless the error is specifically guarded against by getting records from single fingers individually, and (3) the relationships of the moving parts, that is, the total pattern, cannot be adequately approximated.

In spite of its limitations, the apparatus records characteristics, especially frequency, which might prove useful in seeking the origin of tremor, such as striatal or other localized lesions or diffuse metabolic, infectious or psychogenic processes.

Duke University School of Medicine.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

PREGANGLIONIC COMPONENTS OF THE FIRST THORACIC NERVE: THEIR ROLE IN THE SYMPATHETIC INNERVATION OF THE UPPER EXTREMITY. ALBERT KUNTZ and JOHN B. DILLON, Arch. Surg. 44:772 (April) 1942.

In cats and rhesus monkeys the volume pulse wave in the toe or the finger pads was recorded by means of the photoelectric plethysmograph, while an afferent stimulus (ice or faradic stimulation) was applied to one of the lower extremities. Records were taken before operation, after extirpation of the second and third thoracic segments of the sympathetic trunk and after the additional extirpation of the cervicothoracic ganglion. Reflex vasoconstriction was elicited after section of all preganglionic fibers below the first thoracic nerve which are involved in the sympathetic innervation of the upper extremity. Preganglionic components of the first thoracic nerve must, therefore, effect synaptic connections with sympathetic ganglion cells the axons of which extend into the upper extremity. After extirpation of the cervicothoracic ganglion as well, only occasional slight vasoconstriction was elicited from some of the digits. This is explained on the assumption that these efferent impulses were conducted by sympathetic fibers which arise below the third thoracic segment, ascend in the vertebral canal and join the lower cervical and first thoracic nerves. If the conditions in man are comparable to those in the monkey, it is evident that complete sympathetic denervation of the upper extremity cannot be accomplished by any operative procedure which leaves the cervicothoracic ganglion with its gray communicating rami intact and does not interrupt the preganglionic components of the first thoracic nerve.

RASMUSSEN, Montreal, Canada.

SYMPATHETIC DENERVATION OF THE FEET AND LEGS OCCURRING SPONTANEOUSLY OR AS A RESULT OF DISEASE. HARRIS B. SHUMACKER JR., Bull. Johns Hopkins Hosp. 71:1 (July) 1942.

Shumacker studied the effects of denervation on 5 patients, using the following criteria: (1) stability of cutaneous temperature on exposure to cold and inability to influence the cutaneous temperature by such tests as body heating and procaine block of the peripheral nerves; (2) absence of sweating as shown with the Minor test; (3) occurrence of extremely high cutaneous resistance under conditions which favor the lowest possible cutaneous resistance, such as heating the entire body in a heating cabinet until general sweating is profuse.

Both sweating and high cutaneous resistance under the conditions of the test were not found to be absent except when the sympathetic innervation had been interrupted by anesthesia, operation or disease. All 5 patients showed complete loss of sympathetic innervation to various portions of the feet and legs, occurring either spontaneously or as a result of their disease. No correlation was noted between the areas of hypalgesia and the sharply delimited areas of loss of sympathetic innervation, and there was no rigid relation between the degree of vasomotor disturbance and the loss of sensation or muscular power.

The circulation in the feet of some of the patients appeared to be better than the state of calcification and the occlusion of major arteries would have led one to expect. This naturally occurring sympathetic loss should help in the same manner

as does sympathectomy in those cases of occlusive disease with a significant element of vasospasm, if there are sufficient patent blood vessels in the vascular bed to permit an adequate circulation when they are kept in maximal vasodilatation.

PRICE, Philadelphia.

THE BLOOD LACTATE-PYRUVATE RELATION AND ITS USE IN EXPERIMENTAL THIAMINE DEFICIENCY IN PIGEONS. E. STOTZ and O. A. BESSEY, *J. Biol. Chem.* **143**:625, 1942.

It has been found that in a variety of conditions, such as excitement, exercise, anoxia and different degrees of fasting, considerable fluctuation in the pyruvic and lactic acid contents of the blood may occur. Nevertheless, a strict relation between the two is maintained, so that a normal relation can be expressed graphically or by formula. This was found true in human beings, rats and pigeons. Thus, although the actual level of pyruvate or lactate individually can serve as a measure of the aforementioned factors, and under carefully controlled conditions may even reflect true changes in the metabolism of either component, only a deviation in the normal relation between the two components is rigorous proof of a more fundamental disturbance. Therefore the use of this relation eliminates the otherwise difficult decision as to whether a given increase in pyruvate is due to genuine disturbance of pyruvate metabolism or to changes in difficultly controlled experimental conditions. Such a change in the lactate-pyruvate relation of the blood has been noted in pigeons during the course of acute and chronic thiamine deficiency, indicating a pronounced decrease in pyruvate breakdown. The use of this relation has, in fact, made it possible to note a disturbance of pyruvate metabolism early in the course of acute thiamine deficiency and to distinguish with assurance between relatively small degrees of chronic thiamine deficiency in pigeons. Since the colorimetric determination of lactic acid is so simple, even as compared with the pyruvate estimation, it is suggested that both the lactate and the pyruvate level be considered, rather than the pyruvate alone, to determine fundamental changes in pyruvate metabolism.

PAGE, Indianapolis.

THE EFFECT OF CORTICAL DESTRUCTION UPON RESPONSES TO TONES. L. A. PENNINGTON, *J. Comp. Neurol.* **74**:169 (Feb.) 1941.

Pennington studied the effects of restricted bilateral lesions within the auditory areas of the rat's cerebrum on (1) the animal's already acquired level of adaptive performance to a 1,000 cycle tone and (2) the acquisition of adaptive responses to the same tonal stimulus in the untrained animal. Forty-two male albino rats were divided into three groups. In the first group each animal was operated on after the acquisition of the adaptive response to tone. After seven days the animals were retrained to the original stimulus. Seventeen days later some of them were given a second, postoperative retention test. The animals in the second group were trained initially thirty days after bilateral cortical operations in and near the auditory areas had been performed. The animals in the third group served as controls. They were trained and tested in a manner identical with those in the two experimental groups except that no cortical operations were performed. After the completion of the postoperative retention tests the animals were killed and the brains examined microscopically to determine the extent of the lesions. As a result of the study a subordinate region within the auditory cortex was delimited. Analyses of the postoperative retention scores indicated that partially complete bilateral destruction of the subordinate area alone results in reduced efficiency in the auditory problem box. Retention of the adaptive act after postoperative retraining was equivalent to the retention of normal animals. This was evinced by the marked degrees of retardation in initial learning in the case of the animals operated on.

FRASER, Philadelphia.

THE SIGNIFICANCE OF AN ABNORMAL ELECTROENCEPHALOGRAM. DENIS WILLIAMS, *J. Neurol. & Psychiat.* 4:257 (July-Oct.) 1941.

Williams studied 901 subjects to determine the relative significance of an abnormal electroencephalogram in groups of normal subjects and in persons with abnormal states. The electroencephalograms were taken both at rest and after overbreathing. The norm and its deviations were evaluated according to certain criteria of abnormality, which did not differ essentially from those of other investigators. In the normal groups, abnormalities varied from 5 per cent, in highly selected normal subjects (R. A. F. personnel), to 10 per cent, in less carefully selected normal subjects from the army personnel. Abnormal electroencephalograms were present in 26 per cent of a group of psychoneurotic patients, indicating a more frequent constitutional abnormality in such persons than in normal subjects. The percentage abnormality in patients with epilepsy ranged from 55, in subjects with grand mal, to 90, in patients with more than one type of fit. Forty per cent of epileptic patients had a normal electroencephalogram between seizures. According to the author, the abnormalities seen in the electroencephalograms warrant a nonspecific diagnosis of epilepsy, but the recognition of the specific type must be based on clinical observations. In post-traumatic conditions the percentage abnormality varied from 40, in chronic states, to 58, in the more acute states. Seventy-five per cent of the subjects with an abnormal response to hyperventilation showed abnormalities in the resting encephalograms. The author arrives at the following conclusions: 1. An abnormal electroencephalogram in an otherwise normal subject is evidence of an inborn constitutional abnormality involving the central nervous system. 2. This abnormality appears to be nonspecific and may manifest itself in the subject or his offspring as a behavior disturbance, which may be psychoneurotic, psychopathic, psychotic or epileptic.

N. MALAMUD, Ann Arbor, Mich.

THE FUNCTIONS OF THE CEREBELLUM. L. ECTORS, *Confinia neurol.* 4:181, 1942.

Ectors states that the cerebellum functions as a retarding center to which the various motor systems are subordinated. Smooth and striated muscles and tonic and dynamic contractions are under its influence. In every muscular contraction or tonic reaction an impulse is directed toward the cerebellum, and a retarding impulse is returned. This tends to brake the lengthening and shortening of the muscles.

The peculiar histologic character and the uniform structure of the cerebellum can be explained only by a uniform and independent function. The absence of retardation shows itself in the clinical syndrome and in observations on animals in which the cerebellum has been removed. Ectors states that it is possible to construct three main reflex arcs. These are the keys to the various motor reflexes, and their connections occur at the respective motor centers on which cerebellar retardation is exerted. His results are based on known facts and on results of experiments on man and animals with injury to the cerebellum. Extirpation in the *Macacus monkey* produces an increase in the amplitude of the vestibular reflexes. In the cat and pigeon extirpation does not abolish the static reflex.

DEJONG, Ann Arbor, Mich.

THE VALUE OF BROMIDE DETERMINATIONS IN THE DIAGNOSIS AND TREATMENT OF BROMIDE INTOXICATION. M. G. GRAY and MERRILL MOORE, *Confinia neurol.* 4:213, 1942.

Gray and Moore state that the determination of the bromide concentration in the blood has become common as an aid in the diagnosis and treatment of patients with mental disease. There is an individual variation in the capacity to excrete bromides, however, and this and other factors, including the chloride intake and excretion, the dietary intake and the water balance, are all of importance in bromide intoxication. These factors have been overlooked by most investigators.

The bromide level of the blood at which toxic symptoms appear and the extent of chloride replacement vary. Cases have been reported in which persons with an extremely high bromide content of the blood showed no toxic symptoms and others in which bromide intoxication was demonstrated while the bromide level was low. Determination of the blood bromides is valuable when carried out accurately, but because of extreme individual variations it is useless to attempt to correlate the symptoms with absolute bromide levels. Comparison of the chloride and the bromide levels in the blood and urine is more valuable than isolated determinations of the blood bromides, but all laboratory data should be used only as presumptive evidence, the clinical condition of the patient being the more important diagnostic and therapeutic index.

DEJONG, Ann Arbor, Mich.

NITROGEN BALANCE IN PATIENTS SUFFERING FROM MELANCHOLIA. H. I. SCHOU and C. TROLLE, *Acta psychiat. et neurol.* **16**:243, 1941.

Schou and Trolle examined 16 patients with melancholia, 15 of whom were women and 1 a man. All were classified as manic depressive. In 14 of the 16 cases a nitrogen retention of 0.5 to 1.5 Gm. of nitrogen in twenty-four hours was found. During metrazol treatment this retention was further increased. After recovery, either through metrazol treatment or spontaneously, the nitrogen excretion was at the same level as the nitrogen intake. The 2 remaining patients had an increased nitrogen excretion during their melancholia. After recovery the nitrogen excretion equaled the nitrogen intake. The authors conclude that melancholia is apparently associated with abnormal nitrogen metabolism, since in none of their 16 patients were the nitrogen intake and the nitrogen excretion at the same level. These findings were constant in the patients at several examinations, and at no time did a patient change from one type to another.

ADLER, Boston.

THE BEHAVIOR OF MOTOR UNITS IN HEALTHY AND IN PARETIC MUSCLES IN MAN. H. SEYFFARTH, *Acta psychiat. et neurol.* **16**:261, 1941.

Seyffarth found that as fatigue develops in voluntary muscular effort there is a gradual decline in the frequency of discharge of individual motor units in the muscle. This indicates that fatigue is accompanied by progressive inhibition (slowing) of discharge from the anterior horn cells, due either to "primary" fatigue of the cells or to the inhibiting effect of afferent impulses from the acting muscles. Since occlusion of the blood supply of the limb or direct pressure on the mixed nerve to the muscle greatly enhances this decrease in frequency of discharge, the author concludes that the inhibiting effect of afferent impulses from the acting muscles is the more important causal factor.

Seyffarth found that the electrical changes accompanying fatigue are the same in paretic muscles (old poliomyelitis; traumatic palsy) as in normal ones.

BRENNER, Boston.

Psychiatry and Psychopathology

THE ORIGIN AND DEVELOPMENT OF NERVOUS DISTURBANCES EXPERIMENTALLY PRODUCED. W. HORSLEY GANTT, *Am. J. Psychiat.* **98**:475 (Jan.) 1942.

Gantt extended study of the original pavlovian experimental neuroses along three main lines: the production of a chronic anxiety-like neurosis, the early detection of the breakdown by measurements of autonomic function, with the animal under artificial strain, and study of such a state of imbalance, together with the involvement of physiologic systems. He used a classic pavlovian method for inducing conditioned reflexes in animals and then, by the interjection of a

difficult situation based on a strong excitation, induced a conflict. In an acute conflict, the dog showed variations in his general behavior, loss of equilibrium between all the conditioned reflexes and, finally, variations in heart rate and respiration. An incipient nervous imbalance could be detected by measuring the departure from normal in certain autonomic responses. Development of a permanent disturbance under strain tends, at least in part, to have effects on the stability of the animal, for of 3 animals subjected to identical situations of conflict, in 1 a chronic neurosis developed for a period of nine years. Throughout this time the former food signal produced the response of an ordinary dog to actual pain. Any new elements brought into the old environment became capable of producing this response. When exposed to the environment or to the specific stimuli, this animal manifested inhibition of salivary secretion, a respiratory tic or other changes in respiration, tachycardia, intractable pollakiuria and decrease in the time required for sexual reflexes, such as erection and ejaculation. Normal sexual relations have a temporary dissipating effect on the neurosis. The twenty-four hour activity of neurotic animals does not differ from that of the normal. The dog with chronic neurosis was rested for eighteen months in the laboratory, with no effect on the neurosis. He was then transferred to the country for two months, where he showed considerable improvement, but on his being returned to the laboratory, the symptoms gradually reappeared.

FORSTER, Boston.

ELECTROENCEPHALOGRAPHIC STUDIES IN DELINQUENT BEHAVIOR PROBLEM CHILDREN. NORMAL Q. BRILL, HERTA SEIDEMANN, HELEN MONTAGUE and BEN H. BALSER, *Am. J. Psychiat.* 98:494 (Jan.) 1942.

Brill, Seidemann, Montague and Balser made electroencephalographic studies on 28 children with delinquency behavior problems, who varied in age from 7 to 15 years. Two of the children with sexual offenses but no other behavior disorder had normal electroencephalographic tracings. Three children were neglected, and they likewise had no electroencephalographic disorders. Six children were classified as having behavior disorders associated with known or suspected disease of the brain or epilepsy. Of these, all but 1 had abnormal cortical potentials. Six children had behavior disorders with pronounced neurotic or psychotic features, and 4 of these had abnormal electroencephalographic tracings. The remaining 11 children suffered from behavior disorders unassociated with overt organic or functional disorders, and 8 of these had abnormal electroencephalograms.

In view of the high incidence of electroencephalographic abnormalities associated with such behavior disorders (61 per cent of 28 cases), the authors suggest the presence of an underlying cerebral disorder in the majority of children presenting severe behavior problems.

FORSTER, Boston.

DELINQUENCY AND THE ELECTROENCEPHALOGRAPH. WARREN T. BROWN and CHARLES I. SOLOMON, *Am. J. Psychiat.* 98:499 (Jan.) 1942.

Brown and Solomon made electroencephalographic studies on 20 boys committed to a state training school for delinquency. Only 3 of the 20 boys had normal cortical potentials. Eleven had slow, square-topped waves, similar to those seen with psychomotor epilepsy. Three patients presented a subclinical petit mal type of activity, while the remaining 3 showed abnormal cortical potentials not characteristic of either the petit mal or the psychomotor type of disturbance. All patients with severe or moderate degrees of delinquency showed abnormalities of the electroencephalogram. Seven patients with conspicuous behavior difficulties had grossly abnormal electroencephalograms of the psychomotor type and were placed under treatment with dilantin. The results of this therapy are encouraging to date.

FORSTER, Boston.

ALCOHOLISM AND MENTAL DISORDER IN MASSACHUSETTS, 1917-1933. NEIL A. DAYTON, MERRILL MOORE, DOROTHY A. KUNBERGER and M. GENEVA GRAY, *Quart. J. Stud. on Alcohol* 3:50, 1942.

In this study of 56,579 first admissions to mental disease hospitals in Massachusetts, it was found that chronic alcoholism was a prominent factor in about one fifth of the total number. The high point for admissions due to this factor was 1917, and never again during the era of national prohibition did its incidence become as high. In both males and females, chronic alcoholism was most prevalent between the ages of 40 and 49. Single marital status, education, rural habitat, comfortable economic status and native-born parents were all factors associated with a minimal occurrence of alcoholism in this group of patients.

DRAYER, Philadelphia.

ACCULTURATION PROCESSES AND PERSONALITY CHANGES AS INDICATED BY THE RORSCHACH TECHNIQUE. A. I. HALLOWELL, *Rorschach Research Exchange* 6:42 (April) 1942.

Hallowell wished to test the thesis that if there is close connection between the organization of personality and culture patterns, changes in culture should produce changes in personality. The Rorschach technic was used to test exactly to what extent this method, combined with other means of observation, could be used in the study of personality and culture.

The subjects were two groups of Indians; the Lakeside Indians, consisting of 35 men and 23 women, and the Inland Indians, consisting of 30 men and 13 women. In addition, 49 children of both groups were studied. The Inland group was by far the least acculturated and still clung to many native habits. The Lakeside Indians were the most acculturated and had discarded all native customs. The latter group had had the most contact with white men and their ways of living, although the Inlanders also had had some contact.

From the test, it was found that the Inland Indians had pronounced "introversive" tendencies. They were long in answering; their answers were cautious and deliberate; they appeared to be inhibited and showed a fear of self expression. The Lakeside Indians, on the other hand, answered with great speed, which almost averaged that of the white man, and appeared less inhibited. Among the children, however, even the Inlanders nearly approached the speed of white men in answering.

The Inland men were found to be the most introversive, and their women were only less so by a small degree. In the Lakeside group, the men were also the more introverted of the two sexes. Their women had been most affected by contact with white men through intermarriage and had gone far in assuming the habits of the white people.

Personal and social adjustments showed that the women were by far the better adjusted, particularly in the Lakeside group.

MARCOVITZ, Philadelphia.

THE RELATION BETWEEN BLOT AND CONCEPT IN GRAPHIC RORSCHACH RESPONSES. KATE N. LEVINE and JOSEPH R. GRASSI, *Rorschach Research Exchange* 6:71 (April) 1942.

In the graphic Rorschach technic the subject is permitted to present his own drawing of what he sees in each Rorschach blot.

One hundred and fifty subjects were tested and 1,700 drawings were obtained. The presentations varied from exact copies of the blots ("blot-dominated" responses) to drawings which contained none of the outstanding blot elements ("concept-dominated" responses). The former type of drawing always showed a clear picture of the blot and could be recognized easily, but the concept-object was rarely obvious. The latter type of response showed a clear picture of the object, but the blot to which it referred was hard to determine.

On analysis, the subjects who used the "blot-dominated" responses were patients with dementia paralytica, cerebral injury, arteriosclerosis, alcoholism with

encephalopathy and convulsive disorders with demonstrable organic pathology. Deteriorated schizophrenic patients, some depressive patients and some mentally defective persons used this interpretation also, but to a lesser degree. No normal subjects used it. The author explains that the group using this interpretation to the larger degree had lost the ability to abstract and had reacted to the immediate situation presented. The group using this interpretation to a lesser degree did so not from compulsion but from lack of a clear independent concept.

The graphic Rorschach method has made it possible to understand better the responses of the disturbed mental function. MARCOVITZ, Philadelphia.

PSYCHIATRIC PROBLEMS IN MILITARY AVIATION. R. BARRY BIGELOW, War Med. 2:381 (March) 1942.

Psychologic difficulties are the most common cause of flying problems. They commonly cause breakdowns before the flier has had 200 flying hours. Bigelow reviews these difficulties in three situations: the methods of selection of pilots; the difficulties arising during the training period, and the problems arising in active service.

There are no adequate criteria yet known whereby the selection of pilots can be made with any exactness. Those who become successful pilots seem to have three characteristics: (1) a strong desire to fly; (2) a college education, and (3) good judgment. Those who fail as pilots seem to have the following characteristics: (1) an indifferent attitude toward flying; (2) a grade school education, and (3) evidence of emotional instability in their history.

The author advises that in the present state of knowledge, it is important that the applicant's examination include (1) a questionnaire on his life history, (2) the Wonderlic modification of the Otis intelligence test, (3) a personal interview with a psychiatrist, (4) some psychomotor coordination test and (5) the Rorschach test.

Among 1,200 to 1,800 students in training, the following causes of inefficiency were found:

Diagnosis	Student Pilots Referred for Neuro- psychiatric Consultation, January to June 1940	Student Pilots Appearing Before the Advisory Board, January to June 1940
Schizophrenia	2	0
Mild depression.....	2	0
Anxiety state.....	1	1
Paranoid trend.....	0	4
Conversion hysteria		
Predominantly sensory.....	0	3
Predominantly motor.....	2	2
Predominantly visceral.....	2	0
Hypochondriasis	0	1
Phobia	3	1
Obsessive thinking.....	0	1
Psychopathic personality.....	0	1
Constitutional inadequacy.....	1	2
Fear reaction to flying.....	8	8
Fear of failure seriously interfer- ing with performance.....	0	24
No psychiatric diagnosis.....	3	46
	—	—
	24	94

If there was a previous clearcut history of an actual neurosis or psychosis or of a definite trend in that direction, the candidate was usually pronounced unsuitable. Applicants who were borderline and showed a schizoid psychopathy, a mild reactive depression, a tendency to be irritable and to project their difficulties under discipline or criticism, tenseness and anxiousness, conversion symptoms and excessive, but easily relieved, fatigue had to be judged as to flying ability on their individual symptom pictures.

Pilots and ground crews on active service showed much fewer psychologic difficulties than students because they had lost their fear of flying and had no fear of not becoming successful fliers—two difficulties that occurred rather commonly among the student fliers. Their psychologic difficulties were as follows:

Diagnosis	Flying Personnel	Others
Mild depression	1	0
Anxiety state	1	2
Hysteria		
Predominantly psychic	0	2
Predominantly sensory	0	2
Predominantly motor	0	0
Compulsion neurosis	1	0
Psychopathic personality	0	7
Constitutional inferiority	0	3
No psychiatric diagnosis.....	2	1
	<hr/> 5	<hr/> 17

PEARSON, Philadelphia.

Diseases of the Spinal Cord

SPINAL EXTRADURAL CYSTS. FRANK H. MAYFIELD and EVERETT G. GRANTHAM, Surgery **11:589**, 1942.

Mayfield and Grantham add 2 cases of extradural spinal cyst to the 14 already reported in the literature. They suggest that the condition may be more common than the small number of reported cases indicates. The symptoms may resemble those of multiple sclerosis closely, and hence in some cases operation may never be performed.

The cyst in 1 of the cases communicated through its pedicle with the sub-arachnoid space. It was emptied and filled several times at operation before it was removed in order to demonstrate the communication clearly. The authors suggest that such intermittent changes in volume may account for the remission of symptoms often observed in cases of this lesion. Their case supports the hypothesis that extradural cysts arise from herniations of the arachnoid through defects in the dura. The symptoms followed an injury initially, and the authors point out that the dural defect may be traumatic in origin. The second case was notable because of a history of four remissions of symptoms.

In most of the cases described symptoms developed in adolescence. Paraplegia appearing at this time of life should be followed by careful search for evidences of tumor of the spinal cord even though sensory disturbances and pain may be minimal or absent.

DRAYER, Philadelphia.

SYMPTOMATOLOGY AND PATHOLOGY OF SPINAL ARACHNOIDITIS. ADOLF JUBA, Deutsche Ztschr. f. Nervenhe. **152:37**, 1941.

Juba describes 2 cases of spinal arachnoiditis in men aged 57 and 50 respectively. The first patient died four days after operation and the second shortly after operation. Histologic examination revealed chronic proliferative changes in

the meninges, causing obliteration of the subarachnoid space. The spinal cord showed myelin degeneration and disease of the vessels. The author assumes that in the first case the disease developed on a syphilitic basis, since the serologic reactions were positive for syphilis. In the second case the pathologic picture in the spinal cord was classified as subacute necrotic myelitis. Spinal arachnoiditis is considered a syndrome which may be caused by various agents. Operation is indicated when there is evidence of compression of the cord, but the results are dubious. When the disease has progressed to the spinal cord, which seems to occur sooner or later in all cases observed, operation cannot be expected to bring relief. The author advises energetic treatment of the underlying disease whenever possible.

ADLER, Boston.

PATHOLOGY AND PATHOGENESIS OF LANDRY'S PARALYSIS. W. DANSMANN, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **170**:373 (Sept.) 1940.

Dansmann reports 15 cases of Landry's paralysis, 10 with recovery and 5 ending fatally. The author feels justified in including the 10 cases of recovery in spite of the fact that dysphagia was present in only 1. He believes these cases are instances of a milder form of the disease, without involvement of the bulb. In 2 of the fatal cases signs of bulbar disturbance did not appear until three weeks after the onset of the illness. The course of the disease in the cases of the benign form, the absence of febrile reactions and the character of the changes in the spinal fluid favor the inclusion of these cases with those of the more typical Landry's paralysis with a fatal outcome.

All the patients were adults, the youngest being 24 and the oldest 63. There were only 3 women in the series. Only 6 patients gave a history of infection of the upper respiratory tract before onset of the disease. Most of the patients had an acute course, the maximum intensity of the illness coming on not later than a week from the time of onset. In 2 patients, as already noted, the bulbar symptoms appeared after an apparently stationary course of three weeks. The clinical picture was predominantly that of lower motor neuron paralysis. There were, however, some sensory changes in almost every case, often limited to paresthesias and pain. Striking objective sensory changes were absent. In most instances the sensory changes were segmental. No definite level lesion was present in any case. In 1 case the sensory changes were of a peripheral pattern (ulnar and median). The changes in the spinal fluid consisted chiefly of increased protein, with mild or no pleocytosis. There were no clinical changes pointing to cerebral involvement. In cases of the benign form there was usually complete recovery, without residuals.

The anatomic changes were often out of all proportion to the severity of the clinical picture. The disease is mainly one of the peripheral neurons, the anterior and the posterior roots being equally affected. The spinal ganglia were not severely involved. The changes in the peripheral neurons consisted of lymphocytic infiltration, with little change in the axis-cylinders. The changes in the spinal cord and brain were mild and were chiefly perivascular round cell infiltrations, usually lymphocytic. Changes were observed especially around the third ventricle and in the region of the nuclei of the cranial nerves. Changes in the ganglion cells were minimal. In almost all the cases there was some meningeal infiltration over the cerebral hemispheres. There was little evidence of direct spread to the brain. The anatomic changes suggested extension by the blood stream. The author found more cellular infiltration of muscle than has been reported by other investigators.

Dansmann suggests a toxic cause for the diffuse changes described. He does not favor the theory that the illness is a virus infection and offers no suggestion as to the nature of the intoxication.

SAVITSKY, New York.

Peripheral and Cranial Nerves

VITAMIN DEFICIENCIES AND LIVER CIRRHOSIS IN ALCOHOLISM. NORMAN JOLLIFFE, Quart. J. Stud. on Alcohol 1:517 (Dec.) 1940.

Jolliffe concludes from his studies that (a) no alcohol addict with an estimated adequate vitamin B intake had polyneuritis, and (b) every alcohol addict with an estimated absolute deficiency of vitamin B for twenty-one days or more had polyneuritis. Polyneuritis may develop in an alcohol addict as early as the seventh day of estimated absolute deficiency of vitamin B. He states that "alcohol has no direct toxic action (chronic) on the peripheral nerves and that polyneuritis in the alcohol addict is due to vitamin B deficiency." He asserts that the neuropathologic and clinical identity of polyneuropathy and beriberi stands today unchallenged. There is slightly less argument in regard to etiology. While no one doubts the basic nutritional deficiency in alcoholic neuropathy and the avitaminotic nature is also recognized, there are some dissenting views with regard to the specific vitamin involved. The majority of investigators believe the basic etiologic factor is a vitamin B₁ deficiency.

Belief in direct causation of polyneuropathy by alcohol has had to be abandoned in view of the following facts: (a) the identity of "alcoholic" neuropathy and beriberi, (b) the failure of neuropathy to develop in alcoholized animals, (c) the failure of alcoholic neuropathy to develop in adequately nourished alcoholic persons and (d) experimental production by vitamin B₁-deficient diets of the characteristic symptoms in the peripheral nerves and the clinical signs of neuropathy, including the neurasthenic manifestations which, the author states, always precede the onset of peripheral neuropathy.

BRACELAND, Chicago.

SYMPTOMATIC HERPES ZOSTER. CARL MUMME, Deutsche Ztschr. f. Nervenhe. 152:67, 1941.

Mumme describes the case of a man aged 39 whose right testis had been removed because of a seminoma and in whom multiple metastases later developed in the lymph glands and abdominal organs. A paravertebral metastasis had completely destroyed the spinal ganglion of the twelfth thoracic nerve and had grown into the vertebral canal. The twelfth nerve failed to show tumor tissue at autopsy. Seven years after extirpation of the seminoma, and several years after the first metastases had appeared, extensive herpes zoster developed over the right lumbar region and the right thigh, i. e., over the eleventh dorsal to the second lumbar segments. The patient died nineteen days afterward. The spinal ganglia of the eleventh thoracic and first and second lumbar nerves showed inflammatory changes, with many plasma cells. The picture was characteristic of herpes zoster caused by a virus. In the opinion of the author, the metastases of the seminoma favored the growth of the virus and did not cause the herpes zoster.

ADLER, Boston.

A CASE OF SUBACUTE ASCENDING POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION. T. OTT, Schweiz. Arch. f. Neurol. u. Psychiat. 48:83, 1941.

A woman aged 49 had periarthrititis of the left shoulder on first examination. She had always been in frail health and for two years had been subject to attacks of furunculosis. Some months before she had suffered from sciatic neuritis. The periarthrititis subsided nine months later, but soon the furunculosis recurred and injections of autogenous vaccine, which were given for the latter condition, induced mild febrile reactions. A year after the first examination the patient began to complain of weakness in her lower extremities and of pain in the back, legs and tips of the fingers. Examination revealed a sluggish pupillary reaction to light, temporal pallor of the left optic disk, absence of the knee and ankle jerks and anesthesia of the distal type, which was present in all four extremities

but was more pronounced in the lower limbs. Deep sensibility was impaired to a greater degree than was superficial sensation. The calves and nerve trunks were tender on pressure; there was considerable ataxia, and weakness was severe in the lower extremities. The sedimentation rate of the red blood cells was greatly increased, and the spinal fluid contained 1 lymphocyte per cubic millimeter and 2.684 Gm. of total albumin per hundred cubic centimeters. Loss of power later became profound in the upper as well as in the lower limbs, and finally the cranial nerves were affected; swallowing was embarrassed, and temporal pallor of both optic disks was observed. Forty-nine days after the first appearance of weakness signs indicative of massive pulmonary involvement were noted, and two days later there was evidence of serious renal involvement. The patient died fifty-four days after the onset of her last illness.

Autopsy disclosed thrombosis of the left femoral vein, bilateral pulmonary embolism, lipid nephrosis, chronic hypertrophic gastritis and cholelithiasis. Histologic study of the nervous system revealed degeneration without inflammatory reaction in the spinal nerve roots and the posterior ganglia. The degenerative process was especially intense in the lumbosacral roots, with predilection for nerve fibers of large caliber, the myelin sheaths being involved to a greater extent than the axis-cylinders. The peripheral nerves were not examined. Retrograde degeneration of the anterior horn cells of the lumbosacral segments of the spinal cord and ascending degeneration of Goll's tracts were also noted. The blood vessels of the spinal nerve roots, leptomeninges and spinal cord were dilated and filled with blood but showed no other alteration. The cerebral peduncles were not examined; elsewhere in the brain stem the nuclei of the cranial nerves appeared to be normal. Aside from congestion of the blood vessels, nothing remarkable was observed in the cerebral hemispheres. As congestion of the small vessels was not confined to the nervous system, it seemed attributable, at least in part, to venous stasis resulting from failure of the respiratory and circulatory systems. The view is expressed that although infection by a neurotropic virus may have prepared the terrain, the polyradiculoneuritis was primarily of toxic-infectious origin.

DANIELS, Denver.

Vegetative and Endocrine Systems

BLOOD SUGAR IN A CASE OF COMPLETE HYPOPHYSECTOMY. JAMES FINLAY HART and MORTON MAGIDAY, *Arch. Int. Med.* 68:893 (Nov.) 1941.

Hart and Magiday report the case of a 33 year old man who complained of headaches and failing vision for more than two years. Examination indicated that he had a pituitary tumor, and operation was performed in two stages. The surgeons believed that they had performed a complete hypophysectomy when they removed the tumor, a meningioma. About two years later the patient was again admitted to the hospital complaining of visual failure and abdominal cramps. He gave the appearance of being prematurely aged and had a high-pitched voice and feminine distribution of hair. There were marked hyperesthesia and hyperalgesia over the entire body. The fasting blood sugar levels were 80, 45 and 34 mg. per hundred cubic centimeters on different days. The results of sugar tolerance tests were somewhat erratic, with a tendency to a delayed rise and a flat curve.

It has previously been thought that the pituitary gland is essential to life, but recent work has seemed to refute this theory. From their studies on the patient, the authors agree that the pituitary is not indispensable. They suggest that the gland functions as a mechanism to raise the blood sugar level, since its removal produces low blood sugar values without shock and a plateau type of dextrose tolerance curve.

BECK, Buffalo.

TUBERCULOMA OF HYPOPHYSIS WITH INSUFFICIENCY OF ANTERIOR LOBE. JACK D. KIRSHBAUM and HERMAN A. LEVY, *Arch. Int. Med.* **68**:1095 (Dec.) 1941.

Among 14,160 autopsies performed at Cook County Hospital from 1929 to 1940, Kirshbaum and Levy found only 2 cases of tuberculosis of the anterior lobe of the pituitary with symptoms of pituitary insufficiency; yet there were 652 cases of various types of pulmonary tuberculosis and 368 cases of tuberculous meningitis. Neither of the 2 cases of hypophysial tuberculoma occurred in patients with tuberculous meningitis.

In the first case, that of a woman, the criteria for the diagnosis of pituitary cachexia (Simmonds' disease) were fulfilled with amenorrhea, severe asthenia, marked and rapid loss in weight, hypotension, dryness of the skin and hair, low basal metabolic rate and high dextrose tolerance. Autopsy revealed complete destruction of the anterior lobe of the hypophysis by a tuberculous lesion. In the second case, that of a man, signs of pituitary failure, such as a eunuchoid body build with female distribution of hair and hypotension, were present. Autopsy disclosed an old sclerosed tuberculoma of the anterior lobe of the hypophysis, with effects of prolonged pressure on the optic chiasm.

The pathologic picture of tuberculosis of the hypophysis as described by Simmonds may be associated with, or secondary to, the following conditions: (1) acute miliary spread of the disease; (2) nearby meningitis or osteomyelitis of the sphenoid bones, or (3) hematogenous metastasis, with formation of large but slow-growing conglomerate tubercles. The first two types are acute, run a rapid course and generally terminate in early death; they usually do not produce local symptoms, but if local symptoms result they are overshadowed by the general picture of the causative disease. The third type, however, can produce various syndromes as a result of pressure on the pituitary gland and on the surrounding structures, similar to any expanding lesion in this area.

Tuberculosis of the hypophysis is a very infrequent manifestation of tuberculosis of the central nervous system. Pituitary cachexia is rarely due to the destructive effect of tuberculosis, since there are but 3 authentic cases on record, including the case the authors report.

BECK, Buffalo.

THE ELECTRO-ENCEPHALOGRAM IN ADDISON'S DISEASE. W. C. HOFFMAN, R. A. LEWIS and G. W. THORN, *Bull. Johns Hopkins Hosp.* **70**:335 (April) 1942.

Twenty-five patients with Addison's disease were studied with a Grass ink-writing, 6 channel instrument and a kymograph speed of 30 mm. per second. Sensitivity to voluntary hyperventilation was estimated by measuring the time which elapsed before large, slow waves appeared. Sensitivity to low oxygen tension was studied by administering a mixture of 12 per cent oxygen in nitrogen for ten minutes. A dry meter was used to measure the respiratory volume before, during and after the exposure. In 18 of 25 patients definite abnormalities were observed in the resting pattern of the electroencephalogram, which was characterized by the following changes: 1. The presence of oscillations that were slower than the normal alpha rhythm. These had a predilection for the frontal area of the cerebral cortex, and were relatively refractory to the usual effect of opening the eyes. The abnormalities in the resting pattern were typical but cannot be considered pathognomonic, as several other conditions are known to be associated with slowing of the general frequency. 2. Unusual sensitivity of the electroencephalogram to voluntary hyperventilation. This was observed in 15 of 22 patients with Addison's disease and occurred much earlier than in normal persons. 3. Reduction in the incidence of low voltage-high frequency activity (beta waves).

The abnormalities of the electroencephalogram during rest may progress during synthetic "hormone" therapy. Treatment with desoxycorticosterone acetate, aqueous adrenal cortex extract or intravenous infusions of dextrose failed to correct the abnormality in the resting pattern. The high cost of continuous therapy with aqueous adrenal cortex extract precluded administration for a prolonged period.

It was apparent from the study that restoration of blood pressure, plasma volume and electrolytic concentration failed to prevent the occurrence of the electroencephalographic abnormalities in the resting pattern. However, adrenal cortex extract therapy and intravenous infusion of dextrose did in some patients effect a marked reduction in the sensitivity to hyperventilation.

PRICE, Philadelphia.

Treatment, Neurosurgery

CONDITIONED REFLEX THERAPY OF ALCOHOLIC ADDICTION: V. FOLLOW-UP REPORT OF 1042 CASES. WALTER L. VOEGTLIN, FREDERICK LEMERE, WILLIAM R. BROZ and PAUL O'HOLLAREN, *Am. J. M. Sc.* **203**:525 (April) 1942.

Voegtlin, Lemere, Broz and O'Hollaren, in a follow-up report, present additional data on a series of 1,042 cases of alcoholism over an observation period of five and a half years. Among 827 cases, 532 cases of abstinence (58.6 per cent) and 295 cases of relapse (41.4 per cent) were found. In 170 cases in which treatment was given during the most recent six month period (the last half of 1940), the incidence of abstinence was 85.9 per cent and that of relapse was 14.1 per cent. In the original series of 1,042 cases, there were 43 deaths since treatment had been completed. At the time of the original publication of this method, in 1940, about 60 per cent of cures was expected. Of 142 cases observed from four to five and one-half years, cure was effected in 44.7 per cent, cure being defined as total abstinence of alcohol of all kinds for four years after completion of treatment.

MICHAELS, Boston.

THE TREATMENT OF CERTAIN MUSCULAR ATROPHIES WITH VITAMIN E, WITH A NOTE ON DIAGNOSIS AND THE ELECTROMYOGRAMS. H. R. VIETS, E. H. TROWBRIDGE JR. and T. E. GUNDERSEN, *Am. J. M. Sc.* **203**:558 (April) 1942.

Viets, Trowbridge and Gundersen selected 21 patients for treatment with vitamin E in the form of alpha tocopherol acetate, given either by mouth or subcutaneously. Eleven patients with a condition diagnosed as amyotrophic lateral sclerosis, 6 with progressive muscular atrophy and 4 with peroneal muscular atrophy of the Charcot-Marie-Tooth type were treated over a period of ten months, between April 1940 and February 1941 inclusive. The authors believe the diseases in question are syndromes, not only because of their multiple causes but in view of their symptomatic variability. Sensory symptoms of any kind associated with bulbar paralysis, progressive muscular atrophy or amyotrophic lateral sclerosis cannot be accepted, except on the basis of some coincident disease. False reports of recovery following various types of treatment are due in part to the inclusion of patients with sensory symptoms. The diagnosis is based on fibrillations as an unequivocal sign of degeneration of the anterior horn cells or, similarly, of the motor nuclei of the cranial nerves. Reports indicate no beneficial results from the use of vitamin E in cases of amyotrophic lateral sclerosis, progressive muscular atrophy or peroneal muscular atrophy. In general, the weight of the reported cases in the literature is against the value of vitamin E in treatment of the diseases under consideration.

MICHAELS, Boston.

ARTIFICIAL FEVER THERAPY OF JUVENILE NEUROSYPHILIS. J. C. NIELSEN, J. R. MARX and H. A. DICKEL, *Arch. Dermat. & Syph.* **45**:688 (April) 1942.

Five patients of ages from 11 to 20 years were treated by Nielsen and his associates in the Kettering hypertherm. Four of them presented a picture of dementia paralytica and 1 a tabetic picture without the typical dementia paralytica colloidal gold curve of the spinal fluid. Four of the patients were given a complete course of artificial fever. This consisted of fifty hours of treatment in ten

to eighteen sessions at a temperature of 105 to 106 F. One patient received an additional course of thirty hours about two and a half years after the first course. One patient died during the twelfth treatment. Necropsy showed the cause of death to be cerebral edema and subarachnoid hemorrhage. During fever therapy the patients received weekly intramuscular injections of bismuth subsalicylate and intravenous injections of mapharsen. The mapharsen was administered at the height of the fever. After the last fever treatment chemotherapy was continued for six weeks. After this, regular courses of arsenical and bismuth preparations were given up to the time of the report. The 4 surviving patients have been closely followed for one to three and a half years. At the time of writing the 3 patients with dementia paralytica are at home and all have shown definite improvement in both physical and mental activity. The condition of the tabetic patient after one year of improvement has remained stationary, except that the atrophy of his optic nerves has progressed to the point of blindness. The Wassermann reaction of 3 patients returned to normal immediately after therapy and that of the tabetic patient after two years. The normal reaction of 1 of the patients became positive at a later date.

J. A. M. A.

RESULTS OF LOBOTOMIES AT THE DELAWARE STATE HOSPITAL. P. E. ELFELD, Delaware State M. J. **14:81**, 1942.

After experience in 19 cases of lobotomy, Elfeld concludes that "successful results depend not so much on the type of psychoses as on the type of symptoms presented. Those patients who show evidence of agitation, depression, fear, worry, assaultiveness and paranoid reactions seem to have a much better prognosis for social adjustment."

Of the 19 patients, 10 had depressive features. The only truly postoperative death occurred in this group. Six patients returned home and adjusted at pre-psychotic levels. Euphoria and lack of restraint prevented good adjustment of 2 of the remaining patients, and the third became maniacal after the operation. One woman with chronic mania was operated on only three weeks before this report, but seemed much quieter and more cooperative.

Eight patients were considered to have dementia praecox. The 4 patients with paranoid, assaultive trends showed definite improvement, while the other 4, with the simple or hebephrenic type, manifested little change in their condition.

DRAYER, Philadelphia.

SUCCESSFUL OPERATION ON THREE INTRACRANIAL CHOLESTEATOMAS. VIKTOR GRASER, Deutsche Ztschr. f. Nervenhe. **152:13**, 1941.

Graser reports 3 cases of intracranial cholesteatoma. The first patient, aged 31, had right hemiparesis and motor aphasia, which developed suddenly and were accompanied by violent headaches. The left lateral ventricle was displaced downward in the encephalogram, but the arteriogram was not consistent with the diagnosis of glioblastoma. Operation revealed a cholesteatoma which covered the corpus callosum. The author explains the sudden onset of symptoms by disintegration of the tumor or by disturbance of circulation within the area of distribution of the anterior cerebral artery. The second patient, aged 33, had suffered from attacks of vomiting for two years, dizziness and disturbance of gait for one year and ringing in the right ear for one-half year. In addition, there had been dysphagia, headaches and disturbance of vision for two months. Ventriculography revealed hydrocephalus and compression of the fourth ventricle from behind. A cholesteatoma of the fourth ventricle was removed. Two months later, when discharged, he presented only minor signs of cerebellar disturbance. The third patient, a man aged 57, had been slowly deteriorating for many years. Examination showed paresis of the right hand, acalculia, agraphia, apraxia and finger agnosia. An extradural cholesteatoma, which had grown through the bone and displaced the parietal, temporal and occipital lobes, was removed. The postoperative course was uneventful, and the patient recovered completely.

ADLER, Boston.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY AND PHILADELPHIA PSYCHOANALYTIC SOCIETY

O. SPURGEON ENGLISH, M.D., *Presiding*

Joint Meeting, April 10, 1942

Relations of Psychoanalysis to Psychiatry. DR. LE ROY M. A. MAEDER.

Freud said: "Psychoanalysis stands to psychiatry more or less as histology does to anatomy."

Psychoanalysis started within medicine as an attempt to cure hysterical symptoms by psychologic means. Freud developed further the psychologic approach to hysteria begun by Charcot, Bernheim and Breuer. In this country therapeutic psychoanalysis is considered and practiced as a part of clinical medicine.

Psychoanalysis is empiric and scientific. Knowledge of psychologic facts and processes acquired during treatment is the sound basis of its formulations and application in treatment. Psychoanalysis has endeavored to refine and systematize the everyday methods used in understanding the other person's mental situation. In addition to objective observation, it uses introspective psychologic observation. Ernest Jones said that Freud succeeded in fulfilling the delphic injunction, "Know thyself."

Psychoanalysis embodies a dynamic theory of personality, based on a knowledge of clinical psychologic entities and mechanisms. It includes a study of instincts; psychosexual development; ego; superego, or ego-ideal; cultural and environmental effects; mental mechanisms and dynamisms; interhuman relationships, including identification, transference and object relationship, and the structure of personality. It is an instrumentality of research into the mind in health and in disorder.

Psychoanalysis has helped psychiatry eliminate the artificial separation of mental from physical disease, of mental processes from physical processes; it has given impetus to psychosomatic medicine and has emphasized that psychologic factors, such as thoughts and ideas, can and do influence and disturb the function of organs morphologically intact, or bring about changes in them; it has helped psychiatry in its progress from a macroscopic, descriptive science to a microscopic, explanatory one; it has contributed to a better and deeper understanding of criminality, delinquency, behavior problems of children, the psychoses, culture and normalcy; it has developed a more penetrating and effective method for the understanding and treatment of the neuroses; it has, through its basic findings and concepts, penetrated and greatly influenced modern psychiatric thinking and practice.

Reactions of People to the War. DR. GERALD H. J. PEARSON.

Sometime ago the Philadelphia Psychoanalytic Society appointed a committee to collect data on the reactions of people to various phases of the war. This paper is a preliminary report of this committee.

Effect of the War on Children.—So far children show little or no reaction to the war except curiosity regarding certain environmental changes, such as black-outs.

However, in cases in which the family situation has been altered because one or the other parent is absent due to war work, the child shows behavior changes

as the result of feelings of insecurity and of guilt. The results of similar feelings have been found in the life histories of adults who were subjected to similar disturbances in the family constellation during their childhood during the first World War.

Effect of the War on Adolescents.—Adolescents who have a problem in their relationship to their families tend to regard military service as an escape from their problems.

Reactions of Younger Selectees to Military Service.—The majority of selectees feel that it is their duty to serve, although they are not enthusiastic about the causes of war. They state that their fathers are proud that they have been called up but that their mothers are sorrowful. Usually any talk about the war or radio programs dealing with the war have been banned in their homes.

Reactions of Older Selectees.—Some of the older selectees look on military service as a way of having a more interesting life.

Reactions of Patients to Critical Events in the Present War Since Its Start in 1939.—(a) The outstanding reaction was the marked indifference to and disregard of important international crises.

(b) To the attack on Pearl Harbor a number of patients responded with conscious fears lest they be injured or lose something valuable. In some cases this conscious fear was accompanied by an increase in intensity of symptoms; in others, by accentuation of their character pattern. A number of patients began to improve after the initial reaction.

(c) Those patients who showed a reaction to war in general and to specific crises tended to respond according to their childhood response to crises; for example, persons who had tried to solve their childhood difficulties by an isolationist policy showed a similar trend. Patients with a democratic ideology had attempted to solve their childhood problems, i. e., the Oedipus situation, by growing up, but had failed in some manner to accomplish this satisfactorily. Similarly, although they had democratic inclinations, they were unable really to put them into practice. Patients with a pro-Axis ideology had not been able to solve the Oedipus difficulties even as well as those with a democratic ideology.

(d) Female patients often reacted to the black-out with conscious or semi-conscious fantasies of rape.

DISCUSSION

DR. ROBERT A. MATTHEWS: For some time I have been interested in the emotional reaction of inductees and have asked each man examined how he felt about entering the Army. There have been some interesting responses. During the early days of the draft, when the country was not at war, a great many of the men expressed considerable enthusiasm about the service, and approximately 90 per cent answered the question by stating: "I think a year in the Army will do me good." This attitude appeared to be based on a desire to escape from the monotony of everyday life and, at the same time, indicated that only a relatively small number of the men were aware that their military service was probably not going to be limited to a twelve month period. When the length of service was increased to eighteen months, there was an alteration in the attitude to this extent: Many said, "It is probably a good thing for me to be in the Army, but I don't like the idea of being away from home for such a long time." Then, after Pearl Harbor there was a distinct change to a grimmer, less enthusiastic attitude, summed up in the phrase, "Well, I want to do my duty." Of course, there was considerable difference in the attitude of men coming from various social groups.

I have been impressed by the number of inductees who exhibited evidence of anxiety with some degree of autonomic imbalance. Indeed, if all such men were turned down, the percentage of rejections would mount materially.

DR. O. SPURGEON ENGLISH: I believe that the inductees have a definite feeling of cooperation; that there is not nearly so much dissatisfaction as one might expect after reading all the complaints about apathy and complacency. Many of

the men look forward to the Army as a change or relief from the monotony of their present jobs. A great many say, "If I have to go, I have to go." Some say, "Some one has to fight this war—it might as well be me." On the whole, I found few who did not actually want to go. As one got into the more intelligent groups, it was found that they were going from willingness to do their duty. It is my opinion that there is a general willingness to go to war and fight, even though the men are not under the pressure of propaganda which is being spread among the men in the fascist countries.

Ideation and Trends Encountered in Psychotherapy of Manic-Depressive Psychosis. DR. O. SPURGEON ENGLISH.

This paper deals with observations on patients who had suffered from one or more attacks of manic-depressive psychosis and who were receiving psychotherapy in the free interval. Four patients had the depressive and 2 the manic type. In some instances the psychotherapy was orthodox freudian psychoanalysis, and in others it was a psychotherapeutic interview about once a week over a prolonged period. The aim of the study was through verbatim clinical material to bridge the gulf between some of the theoretic considerations of manic-depressive psychosis and the actual management and treatment of patients with this condition so that a more effectual adjustment to life could be made and further attacks prevented. The patient's ideas and emotions are presented under the headings: (1) self esteem; (2) love, including the need for love, as well as the capacity to give and receive love; (3) hate, with the patient's trend in both constructive and destructive aggression; (4) attitude toward body and mind; (5) anxiety and strength to bear it; (6) ambivalence; (7) tendency toward projection; (8) rigidity in thinking, and (9) identification, as well as something of how the patient handled a transference relation.

An important trend found in the personality makeup of patients who fell ill with this psychosis was a great need to be thought perfect in all spheres, such as physical attractiveness, intellectual capacity, wisdom and talent. One patient said, "If I am less than perfect, no one will want to have anything to do with me." Another said, "If I am not doing perfectly I am not doing well at all." These patients tended to use their own ideas of perfection and found it hard to take any behavior values from others. Their conscience and ego ideal were rigid, and they needed help in using a set of more tolerant values with their own.

Those manic-depressive patients who came into a treatment situation seemed to have great difficulty in expressing hostility. They could do this effectively when manic, or indirectly when depressed. Even in their normal interval they might express aggression within the family but had difficulty in being even normally aggressive with those outside the home or with the therapist. One said, "It takes more courage to hate some one else than to hate myself." Another said, "I would rather regard myself as weak and inadequate than blame another." This withholding of aggression, of course, impairs judgment and effectiveness in the everyday life of the manic-depressive person during his "well interval," and because of this weakness certain life situations get the best of him, until they can be solved only by a manic or depressive attack.

These manic-depressive personalities had great difficulty in dealing with love. Their apparent extrovertive friendliness hid great sensitivity. One said, "I can't tell you of the exuberance of having some one care about you or the despair of finding out that they do not." Another said, "When I am depressed I hurt so much all over that any one's friendship or love doesn't matter to me." As already stated, overtures of love cannot be accepted and utilized as readily by the manic-depressive personality as by the normal person, or even by the person with an average transference neurosis. This particular difficulty is one which only a favorable psychotherapeutic relationship can reach and help.

These manic-depressive persons had a great feeling of disgust for their own bodies, for the bodies of others and for body excretions. In this sphere, as well

as in the matter of self esteem, it seems much more difficult to get the manic-depressive patient to modify his opinions of himself than the patient with the ordinary transference neurosis. Like the patient with an obsessional neurosis, he is afraid of showing emotion. One patient said, "When I start feeling love I feel defenseless. I feel myself vulnerable to attack from people." Between attacks the manic-depressive person is not happy, even though he may often appear so.

Although it is too early to show the sustained results of psychotherapy, it is my opinion that prolonged and intensive treatment over a period of two years, more or less, would improve the functioning of the manic-depressive personality in such a way as to make the patient happier, more efficient, a better marital partner and less of a potential carrier of manic-depressive illness to offspring.

DISCUSSION

DR. THEODORE L. DEHNE: For the most part I see patients with real psychoses and rarely have the opportunity to follow manic-depressive patients during the intervals of normal behavior; for that particular reason, Dr. English's presentation was most interesting and educational. Dr. English has definite advantages over a physician who sees only patients with acute illnesses. He sees the manic-depressive patient when he is well or convalescing, or perhaps the illness is just developing, and he can approach the problem slowly and painstakingly, with a great deal of study and care. In hospital practice one must approach the problem more directly and quickly, to get the patient over the period of hospitalization as rapidly as possible. Dr. English sees his patients when they are more or less accessible, but the manic-depressive patient who is ill enough to come to the hospital is, in my experience, almost completely inaccessible. I have no delusional ideas about the value of psychotherapy to a patient who is in the depth of a depression or at the height of a mania. However, hospitalization has much to offer to the patient in the way of good nursing care and removal from the environment that made him ill and from his family, the members of which are probably oversolicitous about him, fearful about him and often much annoyed by him. In hospital practice, one has a great advantage over the consulting psychiatrist in that one sees more patients in a given period than the latter is likely to see and sees the patient at the height of his illness. The more I study the manic-depressive personality, the more the conclusion is impressed on me that generalizations are dangerous. Any fixed notion about the structural concept of the disorder is likely to need a great deal of modification once one attempts to fit the patient's behavior and reactions into a strict structural concept. The picture is always a great deal more complicated than such a concept may permit one to believe.

The prepsychotic personalities of manic-depressive patients are as variable as those of any group one can imagine and cannot be classified under one head by any means whatever. Nor is the patient's hostility or his lack of it, or his aggressiveness or his lack of that, or the presence or absence of any other driving force an ever present factor.

In short, it is my opinion that variations in personality and behavior of manic-depressive patients are so wide that one can generalize about the illness only in a certain limited way.

DR. JOSEPH C. YASKIN: As for the reactions of manic-depressive personalities between attacks, I am afraid I belong to that more rigid school which holds to the concept that the patient shows no lack of emotion between attacks. I wonder whether Dr. English did not have in mind the quality of emotion, rather than the quantity; whether he did not mean that, on the whole, the manic-depressive personality does not lack the necessary quantity of emotion, but that qualitatively it leaves something to be desired. Dr. English accurately described the helplessness and inability to accept help from others, as distinct from the depression occurring in the course of a psychoneurosis.

I should like to hear from Dr. English a little more about his success in preventing manic-depressive psychosis by treatment. I have gone so far as to

make no promises whatever any more. I have seen many persons lead a fairly happy existence, and with little or no provocation break out into an attack of depression or mania. Until the introduction of shock therapy I was not able to make a satisfactory prognosis—the attacks may last three and a half months to two years. How does Dr. English explain his psychoanalytic concepts in the light of the usefulness of shock therapy, which is so successful in the practical management of these patients?

DR. O. SPURGEON ENGLISH: I do not believe that Dr. Yaskin and I would disagree about the quantity of emotion between attacks, except that the manic-depressive person has difficulty in dealing with his emotions and the way in which they are bound together. He cannot say "no" when he should, and he cannot take a positive aggressive step when he should because of fear of being rebuffed.

As for results, I, naturally, cannot say how long these patients will stay well. I shall have to wait five, ten or twenty years to learn what the results will be. In the meantime I believe that the work done with these people has made them more effectual and has kept them living on a higher level, and working more satisfactorily.

What effect electric shock has on the manic-depressive psychosis I cannot say, although I should like to speculate about it. With electric shock there is undoubtedly loss of memory, and many of the patients would be glad to have some of their painful memories erased. I think electric shock does something to put farther from consciousness, to set aside in some way, the unpleasant complexes which keep the depression going on. Undoubtedly the pattern of ideas and their emotional charges are changed, but how I do not know, and I should not attempt to correlate it with what I have said.

Incest and Its Effect on the Participants. DR. PAUL SLOANE.

Since incest in the postadolescent period is not a common phenomenon among civilized people, it was interesting to come across 5 cases in one community within the space of five years. The cases reported were taken from the records of the Family Welfare Organization of Allentown, Pa. The reaction of the girl to the incest situation in each case was studied. The following conclusions seem to be justified as the result of the study. Indulgence in incest in the postadolescent period leads to serious repercussions in the girl, even in an environment in which the moral standards are relaxed. The offender, even though she may have been promiscuous with other men, reacts to incest as if it were socially condemnable and develops a good deal of guilt feeling toward her mother. This is probably related to the death wishes against the latter which are inherent in the incestuous relationship. The attempt to break away from incest leads to forcible types of reaction, the individual nature of which depends on the predisposition of the subject's personality and the relative strength of her ego and superego. In addition to the individual variations, however, one common manifestation appears to be a tendency to act out conflicts by indulging in promiscuous relationships instead of manifesting neurotic symptoms. This promiscuity increases the girl's feeling of guilt, so that she finally must give up even substitute forms of gratification or be prepared to endure ostracism from the fold. Only 1 of the 5 girls could be said to have worked out a satisfactory adjustment; the others showed various degrees of distortion of the personality. This is in contrast to the results found by Rasmussen and Bender and Balu in preadolescent children and can be explained by the increased strength of the superego in the postpubertal years. The destructive effects of incest seem to warrant the severity of the taboos which society has erected against it. (The full paper will appear in a forthcoming issue of the *American Journal of Orthopsychiatry*.)

DISCUSSION

DR. PHILIP Q. ROCHE: Dr. Sloane gives an instructive insight into the ego distortion that comes in his cases of incest. His presentation is devoted largely

to the effect of incest on the female. What effects are noted in male participants? It is my impression that there is a great deal more incest than would be currently indicated by the number of persons in prisons for such offense. Such offenders are almost invariably middle-aged or presenile first offenders who are more often protected by family silence than disposed of by the committing court. Investigation sometimes reveals that their prosecution is inspired less often by outraged morality than by motives of reprisal on the part of other members of the family group or out of interfamily conflicts. In such older offenders, one observes that their behavior is marked by awkwardness, lack of foresight, failure to efface traces and, peculiarly, by indifference after the offense. Incest is not uncommonly a harbinger of a psychotic reaction, which usually develops after imprisonment.

DR. MILTON K. MEYERS: It seems to me that attempts at incest are not rare. About a year ago statistics were compiled from questionnaires sent to women of all classes of society, and a surprising number said they had been attacked by members of their own families. I was astonished to learn that the practice was so common.

DR. O. SPURGEON ENGLISH: I fear that incestuous relations are of more common occurrence than is realized. I understand from social workers to whom I have talked that the father is not often sent to jail. It is difficult, apparently, for the community to take the word of the girl involved and to put the father in jail. One girl I know of has had much difficulty reestablishing good will with her family after she exposed her father. Another feels obliged to tell any man who becomes interested in her about her experiences, after which he has always become too "fresh" with her or has left her entirely. The social adjustment of the girl after being involved in incestuous relations is extremely difficult.

CHICAGO NEUROLOGICAL SOCIETY

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, April 16, 1942

Experimental and Clinical Studies with Methylguanidine Sulfate. DR. JOHN J. MADDEN and DR. LEO A. KAPLAN.

This investigation included animal experimentation, studies on the chemical constituents of the blood and clinical observations on the use of methylguanidine sulfate with 52 mentally ill patients. As outlined in previous studies, methylguanidine sulfate is a nitrogenous metabolite related to creatinine which is regularly found in the blood stream and is excreted in quantities in the urine. In experimental animals it was determined that a shocklike physiologic change could be produced harmlessly by injecting certain concentrations of this chemical intravenously. It was further found that the untoward symptoms (convulsions, prostration, etc.) produced by injection of high concentrations could be promptly controlled by administration of calcium salts. A dose of 75 mg. per kilogram of body weight approached the upper limits of physiologic safety in dogs. With higher concentrations there occurred excessive restlessness, apprehension, respiratory irregularities, pronounced elevation of blood pressure and convulsive muscular movements. Adequate shocklike physiologic responses of less dramatic character took place when much lower concentrations were employed, and lower concentrations were therefore used in the clinical study.

The phenomena observed after injection into experimental animals may be summarized as follows: When methylguanidine sulfate was injected intravenously in doses of from 25 to 75 mg. per kilogram of body weight, an appreciable rise in blood pressure was observed. The elevation values were in direct relation to the concentration of the drug. The return to basal blood pressure was hastened

by injection of calcium gluconate, 10 to 20 cc. of a 5 per cent solution being used. Determinations showed a slowly progressing decrease of blood sugar, which approached the lowest level in the fourth hour and returned to approximately normal in the fifth hour.

In order to determine what pathologic changes might occur after administration of large doses over a comparatively long period, and also to study the acute pathologic changes when a massive lethal dose was given, several dogs were so treated. The pathologic changes were not significant.

In the clinical study, complete and detailed preliminary laboratory examinations and follow-up studies were made, consisting of an electrocardiogram, determination of the basal metabolic rate, and estimations of the nonprotein nitrogen, creatinine, calcium, phosphorus and sugar contents of the blood. An ieteric index reading was made for 20 of the 52 patients, the available facilities precluding this study in every case; in this sampling of the group, no noteworthy deviations from normal were observed during or after the course of treatment.

The doses used with human subjects varied from 15 to 25 mg. per kilogram of body weight, 4 to 7 cc. of a 25 per cent solution of methylguanidine sulfate being injected intravenously. Injections were given five days a week for a series of approximately twenty treatments.

Of this group of 52 patients, 26, or 50 per cent, responded favorably. They were able to leave the hospital and return to their former environment and occupation free from overt symptoms. They may be considered as fully recovered at the date of this report. The mental illness of 43 patients was described as schizophrenia, or dementia praecox; of this group, 23, or 53 per cent, were considered improved. Four patients were classified as having cyclothymic depressions, 3 of whom were favorably influenced by treatment. Five patients whose symptoms were frankly psychoneurotic failed to show any noteworthy improvement.

Approximately 25 other patients were treated during this investigation, but because of factors beyond control, treatment was inadequate; the results in this group are not evaluated. No patient was under treatment more than four weeks, and not more than twenty injections were given in any case.

We believe that this therapeutic method is of definite value in the treatment of functional mental diseases, for the following reasons:

1. None of the disagreeable and dangerous features of the shock therapies is associated with this treatment; hence the therapy may be said to be a pharmacologic one, as opposed to the convulsive treatments or insulin shock.

2. The treatment is more agreeable to the patient; it is without danger, and cooperation from patient and relatives is more easily obtained.

3. The incidence of recovery is comparable to that obtained with shock therapies.

4. The duration of treatment was noticeably shorter than that of the average insulin treatment and was no longer than the period required by the more dangerous convulsive therapies.

5. The simplicity of administration and the cost are commendable features; the cost of the chemical for the therapeutic course is approximately \$3.

6. This therapy is particularly suitable for office and home use, with no need for professional assistance.

DISCUSSION

DR. FRANCIS J. GERTY: The treatment introduced by Dr. Madden and Dr. Kaplan has not been used as widely as some of the more dramatic shock methods. Methods that are physically threatening to the patient seem to be in favor. Since experience has demonstrated that some pretty drastic things can be done with relative impunity, there seems to be an inclination to skirt the edge of danger. Persistence in the use of the less dramatic methods might give better results. Certainly, in some cases good results have been secured.

However, the matter which interests me chiefly is this: From the effects produced by intravenous injection of guanidine, may one not be justified in making

some guess as to the relation of oxygen consumption by the brain to the securing of therapeutic results? The easily observed effects of such an injection are flushing and increase in the pulse rate, blood pressure and respiratory rate. Hypoglycemia also is regularly produced. It is reasonable to suppose that immediately after the beginning of each treatment there is increased oxygen consumption and that for a succeeding period of several hours the utilization of oxygen is decreased. During the initial period the blood flow to the brain must be increased, in view of the effects of increased heart rate and blood pressure during a time in which there is dilatation of the arteries and increase in the respiratory rate, with presumable increase in the amount of tidal air. This would seem to indicate increased oxygen consumption by the brain. Experimental intravenous injections of sucrose and dextrose have been shown to increase the utilization of oxygen. Inasmuch as there is a decrease in blood sugar four or five hours after treatment with guanidine one might expect that there would be a compensatory decrease in utilization of oxygen by the brain during this period. It seems to me that more investigation on the oxygen-carbon dioxide relationship in the brain to all types of shock treatment is indicated and that such studies can best be undertaken with those types of shock therapy in which the assault on the organism is not so violent and extreme that adventitious side effects are produced.

DR. L. J. MEDUNA: There are two factors in this treatment which are remarkable, as Dr. Gerty has emphasized: the increase of blood pressure due to the injection and, at the same time, the decrease of blood sugar. The decrease of blood sugar indicates that the increase of blood pressure is not due to overproduction of epinephrine. If this were the case, one should see an increase of blood sugar at the time the blood pressure rises.

Ten or fifteen years ago methylenediguanidine, under the name of synthaline (decamethylenediguanidine), was recommended in the treatment of diabetes. I do not recall just why its use was discontinued. At any rate, there is at hand a drug which affects the carbohydrate metabolism of the body and brain. I believe that in treatments with continuous narcosis, in various convulsive treatments and in insulin shock the common denominator is the alteration of the carbohydrate metabolism of the brain. It seems that this action is present in the pharmacologic effect of the guanidine also.

Use of methylguanidine is a nonshock treatment. It would seem that the drug should be recommended first in treatment of any functional disease, and if, after a trial of four weeks, it does not bring about improvement, not much time has been lost for the inauguration of other, more drastic treatments.

DR. LEO A. KAPLAN: I should like to add to Dr. Meduna's discussion. Methylenediguanidine was used in Europe under the name of anticoman (a preparation containing pancreatic enzymes, sodium phosphate, tannic acid, bismuth subnitrate and decamethylenediguanidine tartrate) and in the United States as synthaline (decamethylenediguanidine) for the treatment of diabetes. Because it was necessary to use the drug over a long period, several cases of toxic hepatitis resulted, and its use was therefore discontinued. It was also found that calcium salts acted as a physiologic antagonist. In none of the cases was the damage to the liver permanent, and it was relieved by discontinuance of the guanidine and by administration of a calcium salt. In our work the dosage is less, and the period during which the drug is given is short.

With regard to Dr. Gerty's discussion, I should like to say that we did watch the retinal vessels during the injection of methylguanidine and found that they alternately dilated and contracted.

Neuropsychiatric Aspects of Aviation Medicine. DR. M. N. WALSH, Rochester, Minn.

The outstanding symptoms of altitude sickness belong in the domain of neuropsychiatry. A study of the behavior of human beings in low pressure chambers and in high-flying airplanes has demonstrated the fact that a decided individual variation exists with regard to the ability to withstand high altitudes. In general,

however, at an altitude of 6,000 to 9,000 feet (2,000 to 3,000 meters) various compensatory mechanisms involving the circulation and respiration are found. This altitude is known as the zone of reaction. Mental symptoms usually do not occur, although tense or psychoneurotic persons may have sudden syncope, which is not thought to have any relation to anoxemia. The next zone, at an altitude of from 12,000 to 15,000 feet (4,000 to 5,000 meters), is known as the zone of failing compensation. Mental symptoms occur at this altitude, the rapidity of their production depending on the man's susceptibility to altitude sickness, the degree of activity being carried out, the temperature and other factors. It is known that fatigue, alcohol, tobacco and the nervous tension of the flier may greatly influence his power of resistance to the deleterious effects of anoxemia. In this zone there occur a decrease in the acuteness of hearing and vision; blunting of judgment; impairment of critical perception; indolence of thought; forgetfulness and absent-mindedness; unmotivated changes in mood, such as euphoria or depression, and diminution or loss of the will to perform duties, even though tests may demonstrate that the ability to perform the duty is essentially unimpaired. It is important to note that the man himself is often unaware of the decrease in his own efficiency and will continue to feel that he is performing his duty satisfactorily. The great danger of any or all of the symptoms to an airplane pilot is evident.

The next zone is spoken of as the critical zone and lies between altitudes of 18,000 to 24,000 feet (6,000 to 8,000 meters). In this zone the symptoms previously noted in the zone of failing compensation are exacerbated. The patellar reflex increases in amplitude; muscular twitchings occur, followed by local and then general convulsive phenomena; amnesia and, finally, coma occur. The last zone is the lethal zone and is a function of the time when the critical zone is attained. All of the aforementioned reactions are reversible by administration of oxygen, if given in time, and before permanent and irreversible changes in the nerve cells occur.

The time reserve is defined as the period which elapses between the stoppage of an additional supply of oxygen, under conditions of extremely low atmospheric tension, for example, at an altitude up to 40,000 feet (12,000 meters), and the onset of threshold symptoms of failing compensation. This period is a matter of about thirty to sixty seconds at a height of 40,000 feet and of about fifteen seconds if activity is being carried out. Thus, in modern high altitude flying an uninterrupted supply of oxygen is a *sine qua non* in all operations carried out at altitudes above 12,000 feet (4,000 meters), as the pilot who cannot maintain his efficiency at a high level is useless from a military standpoint.

A grave danger to the flyer who operates at high altitudes is the development of gas bubbles in his tissues, called by Armstrong "aeroembolism," or "the bends." This is due largely to the liberation of nitrogen by fatty or fibrous tissue. At an altitude of from 58,000 to 65,000 feet (17,500 to 19,800 meters) the blood "boils" and gas emboli occur. At lower altitudes gas escapes from the tissues and may be dangerous. It is not uncommon in high altitude or low pressure chamber work for acute pains to develop in or near joints, which on roentgenographic examination are found to be due to the accumulation of gas bubbles in the tissues. Armstrong demonstrated the production of gas bubbles in the spinal fluid of animals, and I have been able to show in human beings that at a simulated altitude of 12,000 feet in the low pressure chamber fine, champagne-like gas bubbles escape from the spinal fluid, and this continues for several minutes, up to a simulated altitude of 28,000 feet (8,500 meters). Roentgenograms of human and monkey heads at altitudes of 30,000 and 40,000 feet (10,000 and 12,000 meters) showed no free air in the ventricles of the brain. The breathing of pure oxygen with exercise before ascent will lessen the possibility of aeroembolism. There are on record cases of hemiparesis or hemiplegia, paraplegia and other grave accidents to the vascular supply of the brain under conditions of low atmospheric tensions, presumably due to gas emboli.

The effect of acceleration or rapid change of direction is much spoken of as "black-out." The centrifugal force produced in a cephalocaudal direction by steep

and tight turns and in pulling out of dives may produce cerebral anemia, or even the possibility of structural damage to the brain.

The unusual environment plus the great strain to which the flyer is exposed may produce a chronic fatigue state more rapidly than most other occupations. If the condition is continued, a neurosis may occur. Armstrong has described a special type of neurosis, the so-called aeroneurosis, as it affects experienced flyers. He defined it as a chronic functional disturbance characterized by gastric distress, nervous irritability, fatigue of the higher voluntary mental centers, insomnia and increased motor activity. It is important that a fatigue state be detected in its incipency, since if it is allowed to progress to full development, a long period of rest must be taken, which means loss of the services of a highly trained flier for long periods, or even permanent incapacitation for flying. The rehabilitation of exhausted flying personnel is an activity of great importance, which must be carefully carried out for the best results. The flight surgeon lives with the fliers for the purpose of detecting fatigue states early and giving them prompt treatment. This may not be possible always under war conditions.

DISCUSSION

DR. PETER BASSOE: I do not know anything about aviation medicine, but I have had experience in the past with the effects of compressed air on caisson workers, and I ask myself whether there is not a difference between the phenomena as manifested by aviators and by divers. The man in the airplane starts with a balance of oxygen and nitrogen in his blood and then is subjected to lowering of the air pressure, which causes the nitrogen, being less absorbable, to escape into the tissues; the oxygen is more easily dissolved in the blood. As I see it, the difference lies in the fact that the caisson worker starts at a normal level, then is subjected to an abnormally high air pressure and gets a great deal of gas in solution in his blood; when he comes out too quickly, the nitrogen bubbles appear, and such phenomena as "bends" and "blind staggers" occur. Bubbles may accumulate so as actually to stop circulation at the auriculoventricular orifice. This I do not imagine could happen in aviators, for they never have such an overcharge of gas in the blood. I imagine that the anoxemia factor is greater in aviation while in caisson work the nitrogen factor is more important.

DR. L. J. POLLOCK: Will Dr. Walsh say something of the changes in water vapor in the body at high altitudes? Is that not one of the causes of bubble formation, in addition to release of nitrogen?

DR. MAURICE N. WALSH: Dr. Bassoe is correct in what he says about the difference between the disturbances in caisson workers and those in high altitude pilots. It is true that the pilot starts with normal conditions in his blood and does not have blood gases under pressure, as does the diver. However, I should say that the rapidity with which bubbles develop in the blood or tissues depends on the altitude attained and the rapidity of the climb. Human beings have rarely been exposed to extremely high altitudes; experimental animals, such as goats, have been brought up to 75,000 feet (30,000 meters). Bubbles are present in the cerebral circulation at that altitude. The problem of anoxemia is more important, however, for the air force. Some persons seem to be more susceptible to the effects of high altitude flying.

In reply to Dr. Pollock, the water vapor decreases with other components of atmosphere as one goes higher. So far as I know, the physiologic effect of this decrease has not been studied. Some of the effects which were thought to be due to anoxemia have been demonstrated to result from decrease in carbon dioxide. I believe there is much work to be done, and I regret that neuropsychiatrists have done little. A great deal of investigation has been carried out by physiologists and psychologists with little clinical experience. They have at times a rather biased attitude in trying to apply their observations, with disregard for the fact that human beings do not always conform to rules. I hope neuropsychiatrists in this country will take advantage of the opportunity which is offered.

Book Reviews

Sex Guidance in Family Life Education. By Frances Bruce Strain. Price, \$2.25. Pp. 340. New York: The Macmillan Company, 1942.

This volume is evidence of a healthy trend in present day education. In the preface the author states that the book was written at the request of teachers the country over for a guide to sex education in the schools. Accordingly, it is written so as to offer a long range program, embracing all the grades from the primary to junior and senior high school, with the material arranged and adapted to the expanding sex interest of children from the early years to adolescence.

Throughout the book the author emphasizes both the biologic and the psychobiologic aspects of sexual development and is as much concerned with the dynamics of social and emotional growth as with reproduction. Many practical suggestions are outlined in chapters devoted to methods of gaining community support, matters of organization, family relations, and technics in sex teaching. Special chapters are devoted to the organization of sex guidance counseling centers and the personal and academic qualifications of the counselor.

The book is full of good observations and sensible suggestions. Mrs. Strain says that just as sociologists are able to plot delinquent areas in a city through the presence of delinquency-producing factors, so the sex education worker can plot areas of pornography, for they are found where the public attitude, talk and behavior present the sex life as degraded and degrading. Her experience leads her to state that "constructive sex teaching leads invariably toward the lessening of objectionable activities in school or community."

As would be expected, much of the volume is devoted to child guidance and mental hygiene. In the field of sex education the happy cooperation of the teacher, the biologist, the child psychologist, and the psychiatrist is necessary. Mrs. Strain has indicated a good road in this direction. This book is highly recommended and should be read by all teachers. It is also well worth the attention and interest of the psychiatrist.

Visual Mechanisms. Edited by H. Klüver. Volume VII of Biological Symposia, Jaques Cattell, editor. Price \$3.25. Pp. 322. Lancaster, Pa.: Jaques Cattell Press, 1942.

This collection of papers is an extension of those presented at one of several symposiums on "New Frontiers in Education and Research," held in celebration of the fiftieth anniversary of the University of Chicago, in 1941. In it problems of vision are considered from the physical, biochemical, physiologic, anatomic and psychologic points of view. Each author presents and integrates the material from a series of contributions, the individual study of which would be quite impossible for any one but a specialist in the field. The appearance of such a collection at the present time is particularly opportune in that it provides a base from which investigation can be resumed should its progress falter in these troubled times. For the general reader who desires to acquaint himself with the most recent developments in these varied aspects of vision, as well as for the neurologist who is employing electrophysiologic methods in diagnosis, the individual contributors, Dr. Klüver as editor and the Jaques Cattell Press as publishers have performed a signal service.

AMYOTROPHIC LATERAL SCLEROSIS AND RELATED CONDITIONS

A CLINICAL ANALYSIS

CAPTAIN ROY LAVER SWANK*

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

TRACY J. PUTNAM, M.D.

NEW YORK

The use of vitamin E in the treatment of amyotrophic lateral sclerosis has resulted in a controversy among neurologists. One group of investigators¹ feels that vitamin E cures or arrests the progress of the disease, whereas others² are equally certain that this substance is ineffectual.

In looking for an explanation of this wide difference in opinion the following questions arise: (a) What are the essential features of amyotrophic lateral sclerosis? (b) Are all investigators of this problem using the same criteria for its diagnosis? (c) What is the natural course of the disease when untreated—do all cases progress to death,

* Commonwealth Fund Fellow, 1941.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

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or is it possible that some patients get well or the disease fails to progress after the initial involvement?

In an attempt to answer these and other questions, the following clinical analysis was undertaken. In order to overlook no cases of recovery, as well as to compare amyotrophic lateral sclerosis with other clinically related conditions, cases of progressive muscular atrophy, bulbar palsy and lateral sclerosis were also included in the study.

The following report is based on a study of the records of 151 cases in which the condition was classified as amyotrophic lateral sclerosis, 23 cases in which it was classified as progressive muscular atrophy (all types), 4 cases in which it was classified as progressive bulbar palsy and 19 cases in which it was classified as primary lateral sclerosis. These represent all satisfactory records of these conditions which were observed in the Neurological Institute of New York during the past ten years. A slight reclassification of the cases was made in certain categories as the study progressed, and is embodied in the discussion and the table.

In order to emphasize both their similarities and their differences, each group of cases was first analyzed separately; then, without regard for their hospital diagnoses, all were tabulated together and reclassified on the basis of their chief clinical manifestations, namely, evidence of lateral sclerosis, amyotrophy and muscular fibrillations. The presentation of the following materials is based on this final classification.

AMYOTROPHIC LATERAL SCLEROSIS

I. CLASSIFICATION

The cases of this disease have been classified under three clinical types: the complete, or Charcot; the atypical, and the incomplete. They will be discussed in that order.

A. Complete, or Charcot, Type.—There were 96 readily identified examples of amyotrophic lateral sclerosis which were designated here as being of the complete type. The patients presented well developed evidences of lateral sclerosis, amyotrophy and muscular fibrillations at the time they entered the hospital. There was wasting of the muscles of both upper extremities, most pronounced in the hands, but occurring to a variable extent also in the forearms, the arms and the shoulder girdles. Mild amyotrophy was frequently present also in the lower extremities, and in some instances this was marked. It was not so obvious, however, that the distal parts of the lower extremities suffered more than the proximal. The neck musculature frequently became involved soon after that of the shoulder girdle, but the muscles of the back, chest and abdomen usually suffered later. Fascicular muscular

twitchings³ appeared early, before amyotrophy was evident, and were usually to be seen, off and on, until atrophy had become marked. They were easily identified in the musculature of the shoulder girdles, arms and thighs and could usually be demonstrated in other atrophying muscles as well. Developing bulbar amyotrophy was present in 45 of the 96 cases of the complete type. In 34 instances it followed, and in 11 instances it preceded, the development of amyotrophy elsewhere. Pyramidal tract disease was present in all of the 96 cases of the complete type, although its intensity varied greatly. Many patients exhibited a spastic gait, whereas hyporeflexia, due to advanced amyotrophy, was observed in others. These features will be discussed in greater detail later. No distinction between cases was made on the basis of whether the lesions in the pyramidal tract preceded or followed the amyotrophy, except as will be apparent later in connection with lateral sclerosis with fascicular twitchings.

The examples of complete amyotrophic lateral sclerosis just described conformed roughly with Charcot's original description of the disease.⁴ Many of them would not be considered typical by Charcot, since his description was somewhat rigid. In recent years, however, there has been a tendency to broaden these limits. This is reflected in recent textbooks of neurology.⁵ It should also be noted that relatively few cases of far advanced disease were studied; such cases are to be found more frequently in hospitals for chronic disease.

B. Atypical Type.—Cases of the atypical type presented the essential features of the disease, namely, lateral sclerosis, amyotrophy and muscular fibrillations. However, the distribution of the amyotrophy in all cases, and of the lateral sclerosis in 1 case, was distinctly unusual when the patient entered the hospital. In 5 instances the amyotrophy and fascicular twitchings were present in one extremity (monoplegic type)—in 2 cases in an upper, and in 3 others in a lower, extremity. In 2 of these cases there was beginning, or questionable, slight weakness in one other extremity, but in the other cases no additional amyotrophy, including the bulbar form, could be demonstrated. In these

3. This term is used interchangeably with muscular fibrillations and muscular fasciculations. It is felt that fascicular muscular twitchings, or simply fascicular twitchings, is a more specific term than either of the others. It is intended that it convey the same meaning as Denny-Brown and Pennybacker (*Brain* 61:311-334, 1938) have given to the term "muscular fasciculations."

4. Charcot, J. M.: *Lectures on the Diseases of the Nervous System: Second Series*, London, New Sydenham Society, 1881.

5. (a) Wilson, S. A. K.: *Neurology*, Baltimore, Williams & Wilkins Company, 1940, vols. 1-2. (b) Brain, W. R.: *Diseases of the Nervous System*, ed. 2, London, Oxford University Press, 1940. (c) Grinker, R. R.: *Neurology*, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1934. (d) Bing, R.: *Textbook of Nervous Diseases*, translated by W. Haymaker, St. Louis, C. V. Mosby Company, 1939.

cases there was slight to moderate pyramidal tract disease. Only 1 case of hemiplegic type was noted. In this case the right leg and arm of the patient were weak and wasted, whereas the left extremities appeared normal. There were also early bulbar paralysis, with beginning atrophy of the tongue, and changes referable to the pyramidal tract, most noticeable on the amyotrophic side. In 10 additional cases the amyotrophy and muscular fibrillations were severe in the lower extremities and lacking or slight in the upper extremities (lumbar type). In 2 of these cases mild bulbar paralysis was exhibited. In each of the 10 cases the pyramidal tracts were involved to a variable degree.

Cases of the atypical type just considered have been described by many investigators. A bibliography and a discussion of them are available in Wilson's ^{5a} textbook of neurology. Our follow-up studies and the experiences of others, cited by Wilson, ^{5a} indicate that most of these cases eventually develop into more or less typical examples of the complete, or Charcot, type. It also appears that the so-called lumbar type, in which amyotrophy develops in the lower extremities first, occurs more commonly than is ordinarily believed. In many of these cases the hyperactive reflexes and the positive Babinski sign probably disappear when amyotrophy becomes extreme. The clinical picture then constitutes the pseudopolyneuritic type.⁶ Cases of this type will be considered in detail in the section on progressive muscular atrophy with fascicular twitchings.

Proximal Type: Another group of 5 cases of the atypical form belongs with those in which both the upper and the lower motor neurons are involved, but in them the onset and sequence of amyotrophy were distinctive. In these cases amyotrophy with fasciculations developed in the proximal muscles of the extremities, i. e., in the shoulder girdles in all cases and less frequently in the arms, neck, thighs, hips and back. Later, in a few instances, the forearms and hands became involved. In 2 instances mild bulbar paralysis was exhibited. Pyramidal signs were definite in 4 cases and questionable in 1. Cases of this type have been reported before,⁷ and the disorder is described in textbooks of neurology as the scapulohumeral type.^{5c} According to Dana,⁷ Grinker ^{5c} and observations in the present investigation, the course

6. (a) Patrikios, J. S.: Contribution à l'étude des formes cliniques et de l'anatomie pathologique de la sclérose latérale amyotrophique, Thesis, Paris, no. 149, 1918. (b) Foix, M.; Chavany, and Bascourret: Etude anatomo-clinique d'un cas de sclérose latérale amyotrophique à forme pseudo-polynévritique, *Rev. neurol.* **32**:822-826, 1925. (c) Wohlfart, S.: Die vordere Zentralwindung bei Pyramidenbahnläsionen verschiedener Art; eine histopathologische Untersuchung, *Acta med. Scandinav.*, 1932, supp. 46, pp. 1-235. (d) Friedman, E. D.: Atypical Amyotrophic Lateral Sclerosis, *New York M. J.* **118**:422-425, 1923.

7. Dana, C. L.: Progressive Muscular Atrophy: A Study of the Causes and Classifications, with the Report of an Autopsy, *J. Nerv. & Ment. Dis.* **33**:81-100, 1906.

of this variant of the disease is relatively mild. In 2 of the cases in this series follow-up data were available. In 1 instance the total duration of the disease was sixteen months and in the other ninety-eight months. Another case, not in this series, was recently observed. The patient had been ill for six years and exhibited pronounced atrophy and weakness of the proximal muscles, fascicular twitchings and unilateral pyramidal tract disease, but was able to carry on with his office work six days a week.

Bulbar Type: In 5 additional cases the amyotrophy was limited to (3 cases) or chiefly concerned (2 cases) muscles innervated by cranial nerves. In each of these cases there was mild or moderate involvement of the pyramidal tracts. Follow-up studies revealed that in at least 2 of these cases the more or less complete picture of amyotrophic lateral sclerosis developed before death. It should be pointed out that bulbar signs preceded general amyotrophy in 11 instances of the Charcot type of amyotrophic lateral sclerosis.

In 1 of this group of 5 cases of bulbar involvement the disease presented itself originally with ptosis and diplopia. Later these symptoms cleared up; dysarthria and dysphagia developed, and, finally, amyotrophy appeared in the lower extremities and hyperactive reflexes in all extremities. Von Graefe⁸ first suggested that progressive ophthalmoplegia could be related to the bulbar paralysis of amyotrophic lateral sclerosis. Other investigators have more recently pointed out this relationship, but absence of satisfactory pathologic studies precludes any definite settlement of the problem.^{5a}

C. Incomplete Type.—This type includes three dissimilar subtypes, in which the clinical picture was dominated by evidences of lateral sclerosis, amyotrophy and bulbar palsy respectively.

1. **Lateral Sclerosis with Fascicular Twitchings:** There were 9 cases in this group. The course was rapidly progressive, and the patient exhibited hyperactive reflexes, especially in the lower extremities, frequently bilateral Babinski signs and occasionally absence of abdominal reflexes. In most of the cases a spastic gait occurred; in 6, urgency of urination, and in all but 1, in which the course was of short duration after admission to the hospital, (six months), muscular fibrillations were exhibited. In the last case the course of the disease was rapidly progressive and accompanied by urgency of urination, both of these characteristics suggesting that the case belonged to this group. In 1 case there was questionable bulbar amyotrophy. Subsequent studies revealed that in at least 5 of the 9 cases in this group (all that could be followed) amyotrophy developed before death, and the pres-

8. von Graefe, in Eulenburg, A.: *Lehrbuch der Nervenkrankheiten*, Berlin, A. Hirschwald, 1878, vol. 2; cited by Wilson.^{5a}

ence of fibrillations strongly suggested a similar destiny in 3 others. The inclusion of these cases as instances of a type of amyotrophic lateral sclerosis seems quite justified in view of the ultimate development of amyotrophy in more than half of them. It is of interest in this connection that in 6 of 8 cases of lateral sclerosis studied by Spiller⁹ degenerating ventral horn cells were found at autopsy.

2. Progressive Muscular Atrophy with Fascicular Twitchings: There were 26 cases in this group (19 of them had been diagnosed as instances of amyotrophic lateral sclerosis and 7 as progressive neuropathic muscular atrophy, Aran-Duchenne type). Amyotrophy appeared first in the distal parts of the upper extremities in 12 cases, in the proximal parts of the upper extremities in 4 others, in the lower extremities in 8 cases and in all extremities simultaneously in 2 others. In 5 cases some bulbar involvement, usually slight, was exhibited, and in 2 of these the disease was ushered in by bulbar paralysis. In all cases muscular fibrillations appeared early and were followed and accompanied by muscular atrophy. No definite signs of pyramidal tract disease were found in any of the cases of this group, although in 3 instances they may have been obscured by severe amyotrophy in the lower extremities.

The problem of classifying cases of progressive muscular atrophy is difficult, since the evidences of pyramidal tract involvement, i. e., spasticity and extensor plantar responses, may have been masked by the presence of severe amyotrophy.¹⁰ Furthermore, barely detectable or slight degeneration of the pyramidal tracts may not produce abnormal reflexes. This is indicated by the presence of normal deep reflexes and flexor plantar responses in cases of progressive muscular atrophy in which some degeneration of the pyramidal tracts has been observed post mortem.¹¹ This aspect of the problem has been reviewed recently by Wilson.^{5a} On the other hand, there seem to be a few "pure" exam-

9. Spiller, W. G.: Primary Degeneration of the Pyramidal Tracts: A Study of Eight Cases with Necropsy, Univ. Pennsylvania M. Bull. **17**:390-407, 1904.

10. (a) Ottonello, P.: Sulla sclerosi laterale amiotrofica (Contributo clinico ed anatomo-patologico), Rassegna di studi psichiat. **18**:221, 397 and 557, 1929. (b) Marburg, O.: Amyotrophische laterale Sklerose, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936. (c) Wohlfart, G., and Swank, R. L.: Pathology of Amyotrophic Lateral Sclerosis: Fiber Analysis of the Ventral Roots and Pyramidal Tracts of the Spinal Cord, Arch. Neurol. & Psychiat. **46**:783-800 (Nov.) 1941.

11. Boukis, C.: Zur Frage der spinalen Muskelatrophien, Monatschr. f. Psychiat. u. Neurol. **96**:1-12, 1937. Hassin, G. B.: Amyotrophic Lateral Sclerosis: Anatomic and Pathologic Considerations, Arch. Neurol. & Psychiat. **43**:765-777 (April) 1940; correction, *ibid.* **43**:1056 (May) 1940. Wohlfart and Swank,^{10c}

ples of progressive muscular atrophy in the literature, although none of these have been studied by means of newer methods.¹²

One might be tempted to conclude that there are two distinct groups of cases in which the condition is diagnosed as progressive muscular atrophy, those with lesions of the pyramidal tracts which produce no signs, or in which the signs are masked by amyotrophy, and those in which the older methods of investigation have revealed no degeneration of the pyramidal tracts. The application of newer methods, such as fiber analysis,¹³ to the study of the spinal cords in cases of the latter type may show that in many, if not all, of them degenerated pyramidal tract fibers are present, although sclerosis may not yet be evident. It has been shown in cases of amyotrophic lateral sclerosis that approximately 50 per cent of the large nerve fibers in the ventral spinal roots may be absent before ordinary microscopic examination reveals the defect. This appears to be true of the pyramidal tract areas as well. Moreover, sclerosis may not be observed there, even though a reduction in the number of large nerve fibers can be detected in fiber analysis preparations.^{10c} It must be remembered that the production of glial tissues and of the picture of sclerosis takes time. In the final analysis there will probably be a small number of cases of progressive muscular atrophy with normal pyramidal tracts, and in these instances one may assume that there was insufficient time for degeneration to occur. Under the circumstances it seems expedient to consider progressive muscular atrophy as an incompletely developed phase of amyotrophic lateral sclerosis. The investigators who have expressed themselves both for and against this concept are too numerous to be listed here; the older literature on this subject has been reviewed by Rhein.^{12b}

The problem of classifying primary lateral sclerosis is somewhat similar, since in pure clinical examples of pyramidal tract disease changes in the ventral horn cells characteristic of amyotrophic lateral sclerosis have been shown.⁹ Here, again, studies with the aid of modern methods are lacking.

3. Progressive Bulbar Palsy: There were 3 cases in this group, none with pyramidal disease. In 2 of these cases there was amyotrophy of a slight degree, aside from that in relation to the cranial nerves. In these cases the illness frequently terminates as the result of aspiration pneumonia, so that the complete picture of amyotrophic lateral sclerosis may not have time to develop. As noted before, in 11 cases of com-

12. (a) Alzheimer, A.: Ueber einen Fall von spinaler progressiver Muskelatrophie mit hinzutretender Erkrankung bulbärer Kerne und der Rinde, *Arch. f. Psychiat.* **23**:459-484, 1892. (b) Rhein, J. H. W.: Amyotrophic Lateral Sclerosis: A Pathological Study of an Early Case, *New York M. J.* **105**:915-919, 1917.

13. Häggqvist, G.: Analyse der Faserverteilung in einem Rückenmarksquerschnitt, *Ztschr. f. mikr.-anat. Forsch.* **39**:1-34, 1936. Wohlfart and Swank.^{10c}

pletely developed amyotrophic lateral sclerosis the first manifestation of the disease was bulbar paralysis. The early development of bulbar signs has been noted by other investigators.¹⁴ The theoretic problems are similar to those already considered in connection with progressive muscular atrophy with fibrillations.¹⁵

II. CHARACTERISTIC FEATURES OF AMYOTROPHIC LATERAL SCLEROSIS

A. Fibrillary Muscular Twitchings.—Fibrillations were an almost constant feature of amyotrophic lateral sclerosis, being absent only in the most atrophic muscles. In a few instances, however, they were found only after a diligent search. They appeared early, before weakness or atrophy was evident, and were present until the amyotrophy had become severe. They were observed most frequently in the shoulders, arms and thighs, much less frequently in the hands.

These twitchings appeared to be of great importance in determining the rapidity of the course of the disease, few fibrillations indicating a slow, and many and widespread fibrillations a rapid, course. In 23 cases of completely developed amyotrophic lateral sclerosis with marked and widespread fibrillations the total duration of the disease averaged twenty-seven months, with a maximum variation of from nine to fifty months. In 6 cases with occasional, yet definite, fibrillations the average total duration was fifty-eight months or more (in 3 cases the patients are still alive), with a maximum variation of twenty-four to ninety-six (or more) months. In spite of the fact that the muscular fibrillations observed in the hospital represent only a small "sample" and that fibrillations may vary from time to time, a fairly close correlation of these twitchings with the speed of progress of the disease could be demonstrated.

Pathologic and physiologic studies have shown that many muscle fibers are innervated by a single ventral horn neuron.¹⁶ In amyotrophic lateral sclerosis these groups of muscle fibers degenerate together, producing a pathologic picture characteristic of this disease: groups of muscle fibers in various stages of atrophy surrounded by normal

14. Wechsler, I. S.: Bulbar Amyotrophic Lateral Sclerosis, *Neurol. Bull.* 3:82-86, 1921.

15. Throckmorton, T. B.: Amyotrophic Lateral Sclerosis, *J. Iowa M. Soc.* 7:177, 1917. Rhein.^{12b} Wilson.^{5a}

16. Porter, E. L.: Evidence That the Postural Tonus of Decerebrate Rigidity Increases in Amount by the Successive Innervation of Single Motor Neurons, *Am. J. Physiol.* 91:345-361, 1929. Eccles, J. C., and Sherrington, C. S.: Numbers and Contraction-Values of Individual Motor-Units Examined in Some Muscles of the Limb, *Proc. Roy. Soc., London, s.B* 106:326-357, 1930. Clark, D. A.: Muscle Counts of Motor Units: A Study in Innervation Ratios, *Am. J. Physiol.* 96:296-304, 1931.

fibers.¹⁷ It seems, from the work of Denny-Brown and Pennybacker,¹⁸ that the muscular twitchings in this condition are repeated contractions of these motoneuron units.

Muscular twitchings closely resembling the fibrillations of amyotrophic lateral sclerosis may be seen inconstantly in a variety of conditions. They may be observed occasionally in cases of purulent meningitis, extramedullary tumor of the spinal cord and dementia paralytica^{5a}; syringomyelia, inflammatory lesions of peripheral nerves and progressive hypertrophic polyneuritis^{5b}; paralysis agitans, and infectious polyneuritis, compression of peripheral nerves and debilitating conditions, such as ulcerative colitis.¹⁹ This would seem to indicate that more than one mechanism can produce muscular fibrillations. It has not been proved, however, that the muscular twitchings in each of these conditions are due to repeated contractions of motoneuron units, and it would seem impossible to determine this from clinical examination alone.

B. Signs of Pyramidal Tract Involvement.—In cases of amyotrophic lateral sclerosis signs of degeneration of the pyramidal tract seemed to appear in the following order: hyperreflexia, extensor plantar responses and, finally, absence of cremasteric and abdominal reflexes. The first manifestation was always hyperreflexia in the lower extremities and, later, in the upper. The hyperreflexia usually became pronounced before the next sign of pyramidal tract disease, the positive Babinski sign, appeared. The latter was present in 43 of 112 instances of the completely developed and atypical forms of amyotrophic lateral sclerosis and in 6 of 9 cases of lateral sclerosis with fibrillations. In 31 of the 49 cases with a positive Babinski sign the abdominal reflexes were present, and in the remaining 18 cases they were absent. In another 26 cases the abdominal reflexes were absent and the Babinski sign was negative. The last group of cases was especially difficult to evaluate, as the abdominal reflexes are so frequently disturbed in elderly, and especially in emaciated, persons. Furthermore, degeneration of the peripheral nerves could not be ruled out.

17. Durante, G., in Cornil, V., and Ranvier, L.: *Manuel d'histologie pathologique*, ed. 3, Paris, Felix Alcan, 1902, vol. 2, pp. 1-477. Wohlfart, G.: Untersuchungen über die Gruppierung von Muskelfasern verschiedener Grösse und Struktur innerhalb der primären Muskelfaserbündel in der Skelettmuskulatur, sowie Beobachtungen über die Innervation dieser Bündel, *Ztschr. f. mikr.-anat. Forsch.* **37**:621-642, 1935.

18. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, *Brain* **61**:311-334, 1938.

19. Personal observations and private communications from other observers.

The presence of flexor plantar responses in cases of amyotrophic lateral sclerosis with hyperactive reflexes has been noted before.²⁰ Also, in cases of lateral sclerosis due to *Lathyrus sativus*, Minchin²¹ noted a high percentage of normal abdominal and cremasteric reflexes in patients with both hyperactive reflexes and a positive Babinski sign. This dissociation of the signs of upper motor neuron impairment may be useful in the differential diagnosis of lesions of the pyramidal tract.

Pseudobulbar palsy could be demonstrated in only 1 case. The patient exhibited advanced lateral sclerosis with hyperreflexia, spastic gait, a positive Babinski sign and absence of abdominal and cremasteric reflexes. Fascicular twitchings and emotional instability were also present. In other emotionally unstable patients with advanced pyramidal tract disease, however, pseudobulbar palsy may have been masked by the presence of bulbar amyotrophy.

Urgency of urination was a complaint in 25 cases of amyotrophic lateral sclerosis. In all but 4 of these cases the Babinski sign was positive, and in only 1 case was hyperreflexia the only evidence of impairment of the pyramidal tracts. A clear relationship of urgency to changes in the pyramidal tract was indicated by its presence in 6 of the 9 cases of lateral sclerosis with fibrillation and by its absence in patients with amyotrophy alone. Severe involvement of the pyramidal tracts was not always accompanied by urgency, however, since 4 patients with positive Babinski signs did not complain of this symptom.

Little attention seems to have been paid to urgency in cases of amyotrophic lateral sclerosis. Erb²² noted it in 2 of his cases of lateral sclerosis, and Minchin, in 2 cases of lateral sclerosis due to lathyrism.²¹ It is of interest that urgency occurred in only 1 of 21 cases of primary lateral sclerosis without fibrillations, in contrast to its presence in 6 instances of urgency among 9 cases of the more acute form of lateral sclerosis with fibrillation. Perhaps compensatory mechanisms have time to develop in cases of the more chronic form. Certainly, the presence of urgency in a patient with pyramidal tract disease only suggests that amyotrophic lateral sclerosis may develop. If fibrillations are also present the likelihood is increased.

Emotional instability was frequently associated with degeneration of the pyramidal tracts, although probably not due to it alone. This

20. Chatelin, C.: Le réflexe cutané plantaire en flexion dans la sclérose latérale amyotrophique, *Rev. neurol.* **21**:621-623, 1913. Monrad-Krohn, G. H.: Les réflexes plantaires dans la sclérose latérale amyotrophique, *ibid.* **32**:831-834, 1925. Brunschweiler: A propos du réflexe de Babinski dans la sclérose latérale amyotrophique, *ibid.* **32**:848-851, 1925.

21. Minchin, R. L. H.: Primary Lateral Sclerosis of South India (Lathyrism Without Lathyrus), *Brit. M. J.* **1**:253-255, 1940.

22. Erb, W.: Ueber die spastische Spinalparalyse (tabès dorsal spasmodique. Charcot), *Virchows Arch. f. path. Anat.* **70**:241-267, 1877.

symptom was prominent in 9 cases of pronounced bulbar amyotrophy. In these cases the evidences of pyramidal tract involvement ranged from hyperreflexia to this sign plus extensor plantar responses and absence of abdominal reflexes. In many other cases, however, of just as severe bulbar amyotrophy, and also of marked impairment of the pyramidal tracts, this symptom was not present. One is forced to conclude that although degeneration of the bulbar nuclei, as well as impairment of the pyramidal tracts, is frequently associated with emotional instability in cases of amyotrophic lateral sclerosis, the underlying cause of the emotional instability is probably neither of these pathologic changes.

Davison and Kelman²³ have recently reported a large group of cases of pathologic laughing and crying. Two of their cases were instances of amyotrophic lateral sclerosis, and in a third the disturbance corresponded to what has been referred to here as lateral sclerosis with fascicular twitchings. They concluded that no one region of the brain controls or produces this emotional instability, but that many cortical areas, including the frontal, premotor, motor, parietal, temporal and hippocampal, may be responsible, since they are centers for integration of affective responses. The hypothalamus or other diencephalic nuclei appear to be the main centers for release of these responses, however.

C. Bulbar Amyotrophy.—This feature was noted in 45 cases of the complete, 5 cases of the atypical and 8 cases of the incomplete type of amyotrophic lateral sclerosis (progressive muscular atrophy and fibrillations). Its incidence was roughly the same in each of these conditions, whereas with lateral sclerosis with fibrillations bulbar amyotrophy was infrequently associated (1 case). The muscles innervated by the twelfth cranial nerve were involved in all cases with bulbar amyotrophy. The next most frequently affected muscles were those innervated by the ninth and tenth nerves, then those innervated by the lower part of the seventh nerve and, finally, those supplied by the masticator division of the fifth nerve. In almost all cases involvement of the cranial nerves appeared to be ascending in character, affecting first the hypoglossal nerve, then the glossopharyngeal and vagus nerves and the lower part of the facial nerve and, finally, the masticator division of the fifth nerve. The spinal accessory nerve was not considered with the remaining cranial nerves, since its motor division arises from the cervical portion of the spinal cord and atrophy of the sternocleidomastoid and trapezius muscles was frequently independent of changes in the other cranial nerves.

D. Pain.—Pains, of a varying character, were complained of by more than half the patients, but objective sensory changes were always

23. Davison, C., and Kelman, H.: Pathologic Laughing and Crying, Arch. Neurol. & Psychiat. 42:595-643 (Oct.) 1939.

lacking. Of an unselected group of 45 cases of completely developed amyotrophic lateral sclerosis, cramps and a tightness in the legs were complained of in 12. These seemed to be related to involvement of the pyramidal tracts. A tired or fatigued feeling or a dull ache was complained of in 11 cases, and numbness, coldness or burning, in 6 others. These pains were frequently complained of early, before the true nature of the condition was recognizable, and then were the main source of annoyance. Pain in the lower part of the back and the neck were common in cases of advanced amyotrophy, probably because the joints had lost their muscular support.

Clinical Data in One Hundred and Ninety-Seven

	No. of Cases	Age of Onset (Years)							Sex Incidence		Urgency of Urination	Emotional Instability	On Admission to Hospital								
		10	20	30	40	50	60	70—	M	F			½	1	2	4	6	8	10	11—	
Primary lateral sclerosis.....	21	2	1	..	6	6	5	1	8	13	1	1	..	3	..	7	2	2	4	3	
Amyotrophic lateral sclerosis																					
Lateral sclerosis with fascicular twitchings.....	9	2	3	3	1	3	6	6	1	4	3	1	1	
Complete type (Charcot)...	96	3	21	29	31	12	73	23	18	8	22	34	24	11	
Atypical form *.....	16	1	1	6	7	1	12	4	2	0	2	8	3	3	
Proximal type.....	5	1	1	2	1	5	0	1	0	2	1	2	
Bulbar type (with evidences of pyramidal tract degeneration).....	5	2	2	1	2	3	0	2	2	3	
Progressive bulbar palsy...	3	3	..	1	2	0	0	2	2	
Progressive muscular atrophy with fascicular twitchings.....	26	2	4	7	9	4	22	4	0	0	7	8	7	4	
Progressive muscular atrophy without fascicular twitchings.....	16	4	7	1	2	1	12	3	0	0	2	3	4	2	2	2	

* Atypical forms include the monoplegic, hemiplegic and lumbar. The proximal type has been considered separately because the incidence of elevated protein was unusually high in cases of this form.

These subjective sensory complaints have been frequently remarked²⁴ and are considered of unusual occurrence.^{5d} Their source is not at all clear, but possibly products of degeneration or of abnormal metabolism, which arise from the degenerating motor nerve fibers or muscle fibers, stimulate the neighboring sensory nerve fibers. Compression of sensory nerve fibers by contracting connective tissues which are replacing degenerated motor nerve fibers could also be a factor late in the disease, but probably not at its beginning.

E. Cerebrospinal Fluid Proteins.—The proteins of the cerebrospinal fluid were elevated above 40 mg. per hundred cubic centimeters in 55 cases of amyotrophic lateral sclerosis, and in 37 instances the protein

24. Wechsler, I. S.; Brock, S., and Weil, A.: Amyotrophic Lateral Sclerosis with Objective and Subjective (Neuritic) Sensory Disturbances: Clinical and Pathologic Report, Arch. Neurol. & Psychiat. 21:299-310 (Feb.) 1929. Bing.^{5d}

content was greater than 50 mg. per hundred cubic centimeters. The table shows the changes in the cerebrospinal fluid proteins which were observed in each type of the disease. It appears from the data that the proteins were affected more by lesions in the peripheral nerves than by those in the pyramidal tracts and that bulbar amyotrophy alone was associated with minimal changes in this substance. In 12 cases in which the proteins were above 70 mg. per hundred cubic centimeters there was severe general amyotrophy, whereas pyramidal signs were variable or absent (2 cases). In 6 of these cases there was severe, in 1 mild and in 5 no bulbar paralysis. The duration of the disease in

Cases of Amyotrophic Lateral Sclerosis and Related Conditions

Duration of Disease (Years)															Cerebrospinal Fluid Proteins (Mg./100 Cc.)					
At Death							In Patients Still Living								40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	90 and Above
1	2	4	6	8	10	15	4	6	8	10	15	20	25	30						
..	1	1	..	1	2	2	3	3	..	1	..	2	1	..
..	2	3	2	..	2	3
3	13	12	5	4	5	3	1	..	1	10	11	6	3	5	2
..	3	4	1	1	1
..	1	1	2	2	1
..	2	1
..	..	1	1
1	3	3	2	1	3	1	1	1	3	1	1	..
..	1	..	1	1	3	1	3	2	3	1	..	1	1	..

these 12 cases varied from three to thirty months, in 7 cases being less than one year. In 6 of the 7 cases in which the illness was of one year's duration or less bulbar amyotrophy was severe.

In a group of cases of amyotrophic lateral sclerosis Merritt and Fremont-Smith²⁵ found the protein content of the cerebrospinal fluid elevated much as reported here. In all other respects, essentially, the cerebrospinal fluids were normal in both series of cases.

F. Vital Data.—These data, of which little unusual can be said, are presented in the table. The age of onset of amyotrophic lateral sclerosis was chiefly during the fourth, fifth and sixth decades of life. The sex incidence was approximately 3 males to 1 female, except in cases of lateral sclerosis with fibrillations and bulbar palsy, with or without involvement of the pyramidal tracts. In these cases there was a tendency

25. Merritt, H. H., and Fremont-Smith, F.: *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1937.

for females to be more numerous than males. There was a somewhat higher incidence of amyotrophic lateral sclerosis among Jewish patients than would have been expected from the incidence of their admission to this hospital. This was especially noticeable in the complete, or Charcot, type. Otherwise, the racial incidence was not unusual, and almost all racial groups except the Chinese were represented. Reed²⁶ stated that the disease occurs with ordinary frequency in the Chinese.

Associated diseases were conspicuous by their infrequency. Diabetes mellitus occurred in 4 cases; secondary anemia, of unknown origin, in 2 cases; questionable pernicious anemia, in 1 case; hypertension, in 1 case; brain tumor, in 1 case; syphilis, in 1 case; osteoarthritis, in 1 case, and chronic myelitis, in 1 case. These conditions either had preceded or were present simultaneously with amyotrophic lateral sclerosis. Trauma was also conspicuous by its infrequency; in only 1 instance was there a clear time relation between the occurrence of appropriate injury and amyotrophy. Trauma frequently occurred after the onset of the disease, and then was due to the patient's motor impairment. Trauma as a causative factor has been investigated and discussed by others,²⁷ and it can be said that there is no clear or constant etiologic relationship between it and the onset of amyotrophic lateral sclerosis in this series.

Many years before the onset of what appeared to be amyotrophic lateral sclerosis, 3 patients, not included in this analysis, had had encephalitis, and 2 others, acute poliomyelitis. Salmon and Riley²⁸ have recently discussed the relationship of acute poliomyelitis to subsequent chronic amyotrophy. The present study has not materially clarified the relationship.

PRIMARY LATERAL SCLEROSIS WITHOUT FASCICULAR TWITCHINGS

Twenty-one cases have been included in this group. They were distinguished from the examples of acute lateral sclerosis with fibrillations by the very gradual, or insidious, onset of signs and symptoms of pyramidal tract disease. Hyperreflexia appeared first in the lower extremities in all cases. Later, in all but 7 signs of pyramidal involve-

26. Reed, A. C.: *Nervous Diseases in China*, Boston M. & S. J. **171**:638-643, 1914.

27. Waggoner, R. W., and Löwenberg, K.: *The Role of Trauma in Amyotrophic Lateral Sclerosis*, *Tr. Am. Neurol. A.* **65**:84-92, 1939. Turner, J. W. A.: *Trauma and Progressive Muscular Atrophy*, *Lancet* **2**:549-551, 1939.

28. Salmon, L. A., and Riley, H. A.: *The Relation Between Chronic Anterior Poliomyelitis or Progressive Spinal Muscular Atrophy and Antecedent Attack of Acute Anterior Poliomyelitis*, *Bull. Neurol. Inst. New York* **4**:35-63, 1935.

ment were present in the upper extremities, and in 1 pseudobulbar palsy with emotional instability developed. In all but 3 cases in this group extensor plantar responses were elicited, and in 11 of these abdominal reflexes were absent. Muscular fibrillations and amyotrophy were observed in none of these cases, and in only 1 was urgency of urination complained of. The course of the disease was slowly progressive, having a duration of more than five years in 11 cases and of more than ten years in 6 cases at the time the patient entered the hospital. In only 1 instance was the involvement of the pyramidal tract unilateral, as in the cases described by Mills.²⁹

In many respects the evidences of impairment of the pyramidal tract in these patients were similar to those observed in amyotrophic lateral sclerosis. The signs were ascending in that they appeared in the lower extremities first and in the upper extremities later. In both conditions the order in which the neurologic signs developed was the same, i. e., hyperreflexia, extensor plantar reflexes and, finally, absence of abdominal reflexes. In cases of amyotrophic lateral sclerosis the chief distinguishing features were urgency of urination and the very rapid course. It is possible that urgency did not appear in cases of the more slowly developing lesions of the pyramidal tract because compensatory mechanisms had time to develop. The fact that the cerebrospinal fluid proteins were elevated to 88 mg. per hundred cubic centimeters in the 1 case in this group with urgency suggests that the course of the disease had recently become rapidly progressive and that perhaps amyotrophy would appear later. It is of considerable interest that the development of pyramidal signs in posterolateral sclerosis, as well as in amyotrophic lateral sclerosis, is similar.³⁰ An interesting discussion of the relationship of lateral sclerosis to amyotrophy on the one hand, and to posterior column disease, on the other, was given by Strümpell.³¹

A few facts relative to vital data are of interest. In cases of lateral sclerosis, with or without fibrillations, females were afflicted more frequently than males. Also, the incidence of both conditions in Jewish patients was lower than would be expected from the incidence of Jews admitted to this hospital. There was considerable variation in the age of onset in cases of lateral sclerosis without fibrillations, although in most cases the onset was in the fourth, fifth or sixth decade.

29. Mills, C. K.: Unilateral Ascending Paralysis and Unilateral Descending Paralysis, *J. A. M. A.* **47**:1638-1645 (Nov. 17) 1906.

30. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, *Brain* **52**:271-291, 1929.

31. Strümpell, A.: A Textbook of Medicine, translated from the thirteenth German edition by H. F. Vickery and P. C. Knapp, third American edition, New York, D. Appleton and Company, 1901.

In recent years there has been a tendency among neurologists to doubt the existence of pure examples of lateral sclerosis (aside from familial types). This tendency is to a limited extent supported by Spiller's⁹ study of 8 cases, which clinically were examples of lateral sclerosis. In 6 of these, degenerating ventral horn cells were noted; in only 2 cases were the pathologic changes limited to the pyramidal tract areas. Erb,²² Strümpell³¹ and other early investigators expressed the belief, on the basis of pathologic studies, that pure cases of lateral sclerosis did exist, although in many instances clinically pure cases were shown later to be examples of posterolateral sclerosis or amyotrophic lateral sclerosis. Recent investigators seem to believe that modern methods of study would disclose even fewer examples of "pure" lateral sclerosis. Here, again, Wilson^{6a} pointed out the gross absence of any such studies. Final judgment must be reserved, although it seems quite likely that a limited number of "pure" examples of lateral sclerosis do occur. For the purpose of prognosis it is of considerable value to recognize the clinical examples of this condition, since then life expectancy of the patients is much greater than is that of patients with lateral sclerosis plus muscular fibrillations.

PROGRESSIVE MUSCULAR ATROPHY WITH FEW OR NO FASCICULAR TWITCHINGS

There were 16 cases in this group. They were distinguished from cases of progressive muscular atrophy with fibrillations (incompletely developed amyotrophic lateral sclerosis) by an insidious onset and a slowly progressive course. The main feature in this group was amyotrophy. This appeared first in the distal parts of the extremities, and there became extreme. Usually muscular atrophy failed to progress central to the knee or lower portion of the thigh, in the lower extremities, and to the hand or forearm, in the upper extremities, so that spindle deformities resulted. In all cases the legs were involved, and in many the hands and forearms as well. Twice the lower and upper extremities became involved simultaneously. In 2 cases the trapezius, erector spinae and sternocleidomastoid muscles were also atrophic, so that the patient's head bobbed around like a ball balanced on the end of a seal's nose. In 3 instances deformities of the feet, i. e., equinovarus and pes cavus, were noted. These had appeared early and were well developed before much attention was paid to them.

The slowly progressive nature of this condition is illustrated in a case in which an interval of thirteen years occurred between involvement of the legs. Seven years later the hands became involved as well. Usually, however, both legs became affected within a year, and the hands as well within three to five years. After this initial involve-

ment of the extremities, further progress of the developing amyotrophy appeared to be arrested, and the patient's condition remained almost stationary, in many instances for years. All but 2 of the patients followed at this institute during the past ten years are still alive and little changed from the time they first entered the hospital. One of them died after an operation for gallstones. In the other patient the course of the disease had been slowly progressive for about six years. Fascicular twitchings were then noted in the shoulders for the first time, and in less than two years the patient died. This patient also exhibited hyperactive reflexes, a positive Babinski sign on one side and diminution in objective peripheral sensitivity of the extremities.

Fibrillations were notably absent in 12 and inconspicuous in 4 of these cases. Evidences of pyramidal tract disease were observed in 3 cases. These consisted of hyperreflexia in the lower extremities in 1 case, extensor plantar responses in another and hyperreflexia, extensor plantar responses and absence of the lower abdominal reflexes in the third. Urgency of urination was not noted in any case. It is worth while to point out that signs of involvement of the pyramidal tract developed in the same order in these cases as in cases of amyotrophic lateral sclerosis, only more slowly. In 3 instances, in all of which pyramidal signs were absent, the cerebrospinal fluid proteins were elevated to 51, 78 and 100 mg. per hundred cubic centimeters respectively. This increase appeared to be of no prognostic value.

Subjective sensory complaints were frequent, and objective sensory changes, usually with stocking and glove distribution, were observed in 4 cases. From the fact that the objective changes were demonstrated only after long-standing weakness and severe amyotrophy, it is possible that these sensory phenomena were secondary to degenerative and reparative changes which were taking place in the peripheral nerves. Presumably, the degenerated motor nerve fibers were gradually replaced by scar tissue. This tissue contracted and exerted pressure on the sensory nerve fibers, and sensory phenomena, both subjective and objective, resulted. This concept is not supported by the occurrence of peripheral sensory changes in cases of so-called scapuloperoneal amyotrophy,³² since the amyotrophy in the upper extremities is proximal and separated from the area of sensory change by a variable distance.

The incidence of males in these cases was relatively high, 12 males to 4 females, and the racial incidence was not remarkable. The age of onset was early, before the twentieth year in 11 cases. The influence of heredity was apparent in 5 of the 16 cases, in 2 of which other members of the family were affected. In these cases the age of onset and

32. Davidenkov, S. N.: Scapuloperoneal Amyotrophy, *Arch. Neurol. & Psychiat.* **41**:694-701 (April) 1939.

the sex and racial incidences were not different from those for the group as a whole. However, the cases with a hereditary background were different from the remaining cases in the group in one particular, in that in 3 of them there were foot deformities, mentioned before. In 2 there were no such deformities.

In the 5 cases in this group with a hereditary background the disorder corresponded closely with the condition designated by the term peroneal, or the Charcot-Marie-Tooth type of progressive muscular atrophy.³³ In 3 of these cases foot deformities were noted, and in 2 objective as well as subjective sensory changes were present. In all other respects, with the possible exception of speed of progress, which cannot be checked now because all but 2 of the patients who could be followed are still alive, these cases were not to be definitely distinguished from the remaining 11 cases of nonhereditary disease. It should be noted that objective sensory changes were also demonstrated in 2 of the cases of the nonhereditary form.

A review of the literature relative to examples of the hereditary or familial form of progressive muscular atrophy (progressive muscular atrophy with few or no muscular fibrillations) revealed two noteworthy facts.³⁴ First, an extremely insidious onset of foot deformities is com-

33. Charcot, J. M., and Marie, P.: Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, debutant par les pieds et les jambes et atteignant les mains, *Rev. de méd.* **6**:97-138, 1886; cited by Symonds and Shaw.^{34c} Tooth, H. H.: The Peroneal Type of Progressive Muscular Atrophy, Thesis, Cambridge, London, H. K. Lewis, 1866; cited by Symonds and Shaw.^{34c}

34. (a) Siemerling, E.: Zur Lehre der spinalen neuritischen Muskelatrophie (*Atrophia muscularis progressiva spinalis neuritica* Bernhardt), (progressiven neurotischen oder neuralen Muskelatrophie Hoffmann), *Arch. f. Psychiat.* **31**:105-127, 1898. (b) Virchow, R.: Ein Fall von progressiver Muskelatrophie, *Virchows Arch. f. path. Anat.* **8**:537-540, 1855. (c) Symonds, C. P., and Shaw, M. E.: Familial Claw-Foot with Absent Tendon Jerks: A "Forme Fruste" of the Charcot-Marie-Tooth Disease, *Brain* **49**:387-403, 1926. (d) Eisenbud, A., and Grossman, M.: Peroneal Form of Progressive Muscular Atrophy, *Arch. Neurol. & Psychiat.* **18**:766-778 (Nov.) 1927. (e) Cavanaugh, W. J., and Tucker, H.: Progressive Neural Muscular Atrophy (Peroneal Type): Clinical Report of Two Cases in Brothers, Associated with Mental Symptoms, *New Orleans M. & S. J.* **81**:290-293, 1928. (f) Lhermitte, J., and Mouzon, J.: Amyotrophie du type Charcot-Marie à debut tardif. Prédominance familiale dans le sexe féminin, *Rev. neurol.* **67**:243-248, 1937. (g) Brownsberger, C. N., and Nielsen, J. M.: Progressive Spinal Muscular Atrophy with Sensory Changes: Possibility of Two Diseases, *Bull. Los Angeles Neurol. Soc.* **3**:182-185, 1938. (h) Schneider, D. E., and Abeles, M. M.: Charcot-Marie-Tooth Disease with Primary Optic Atrophy: Report of Two Cases Occurring in Brothers, *J. Nerv. & Ment. Dis.* **85**:541-547, 1937. (i) Ingham, S. D.: A Case of Transition Between Charcot-Marie-Tooth and General Form of Progressive Spinal Muscular Atrophy, *Bull. Los Angeles Neurol. Soc.* **3**:136-137, 1938. (j) Fitzgibbon, J. P.: Atypical Charcot-Marie-Tooth Disease Following Probable Poliomyelitis, *ibid.* **4**:136-138, 1939.

monly the initial manifestation of the disease. This was usually noted early in childhood or infancy. Notable exceptions to this rule are a case described by Lhermitte and Mouzon,^{34f} with onset at the age of 52, and 1 case in this series, with onset at the age of 30. Second, cases of the familial type are apt to present features not ordinarily considered as a part of the general picture of progressive muscular atrophy—for example, optic atrophy,^{34h} posterior column disease,³⁵ mental changes,^{34e} nystagmus^{34h} and scapular amyotrophy.³² The sensory changes, said by Charcot, Marie and Tooth to be of infrequent occurrence, need no further emphasis. In a few cases evidences of pyramidal tract disease were also present.³⁶

In commenting on the foot deformities, Symonds and Shaw^{34c} stated that if the intrinsic muscles of the feet are affected first pes cavus develops, and if the peroneal and anterior tibial groups are involved first equinovarus results. These authors also pointed out that in the main postmortem examinations have been unsatisfactory and few, and have revealed a variable pathologic picture combined with degeneration of the anterior horn cells and of the ventral motor nerve roots. A study by Macklin and Bowman³⁷ of a family composed of 101 persons showed that approximately 50 per cent of the offspring of parents with the disease became afflicted.

The remaining 11 cases without hereditary or familial features appear to be cases of arrested amyotrophic lateral sclerosis, 8 of which were instances of the incompletely developed disease and might well be examples of slowly developing progressive muscular atrophy, and 3 of which might be examples of an arrested or slowly progressive form of the complete, or Charcot, type. In all of these cases muscular fibrillations were absent or inconspicuous. This is of interest in view of the fact that in cases of amyotrophic lateral sclerosis with few fibrillations the prognosis is better than in those with many fibrillations.

The relationship of the hereditary to the nonhereditary forms of progressive muscular atrophy with few or no fibrillations is uncertain. Clinically the cases may be similar, a transition from one form to the other being supplied by the 2 cases of nonhereditary type with sensory changes and the 2 cases of hereditary type without foot deformities. Although the fact is not clearly demonstrable here, a study of the literature and consideration of the cases included in this study indicate that the hereditary form of the disease was somewhat less rapidly progressive than the nonhereditary form. Also, the amyotrophy in cases of

35. Siemerling.^{34a} Virchow.^{34b} Schneider and Abeles.^{34h}

36. Brownsberger and Nielsen.^{34g} Ingham.³⁴ⁱ

37. Macklin, M. T., and Bowman, J. T.: Inheritance of Peroneal Atrophy, *J. A. M. A.* 86:613-617 (Feb. 27) 1926.

the hereditary form tended to be limited to the more peripheral parts of the extremities. In both these respects an indistinguishable transition from one type to the other was present, and notable exceptions were encountered. In none of our cases of the hereditary form were evidences of pyramidal tract disease observed, but elsewhere,³⁶ as noted before, this has been reported.

COMMENT

Amyotrophic lateral sclerosis may be considered to be a steadily progressive, fatal disease of approximately one to six years' duration. Our data (table) do not indicate that its various clinical types, i. e., complete, incomplete and atypical, differ notably in their course, although it must be said that the prognosis increases in gravity as the clinical picture becomes more complete. This is to be expected, since the atypical form and in many cases the incomplete form become complete before death. The cerebrospinal fluid proteins were not always a reliable index of progression of the disease. It is true that elevation of proteins occurred in most of the cases of more rapidly progressive course, but in many cases of slowly progressive course this increase was also exhibited. The appearance of bulbar palsy must always be viewed with alarm, since this makes feeding difficult and may lead to the development of aspiration pneumonia.

The frequency and magnitude of muscular fasciculations appeared to be a reasonable indication of the speed of progress of the disease. As pointed out before, many fascicular twitchings indicated that the amyotrophy was developing rapidly, whereas few fibrillations were seen when it was more slowly progressive. It should not be forgotten, however, that only a small "sample" of fibrillations could be observed during the patients' stay in the hospital. Quite possibly, the fibrillations may have been entirely different either before or after this period. Despite this obvious source of error, a fairly close correlation could be demonstrated. This should be of value in prognosis, especially when patients can be observed from time to time over a longer period.

The prognosis in cases of either primary lateral sclerosis or progressive muscular atrophy without muscular fibrillations was surprisingly good. It is worth mentioning that the cerebrospinal fluid proteins were elevated in 3 cases of progressive muscular atrophy without fibrillations, the course of the disease in these cases being no different from that in the other cases in this group with normal cerebrospinal fluid proteins.

It was noted earlier in this paper that the 11 cases of nonhereditary progressive muscular atrophy without fibrillations might conceivably be instances of arrested or very slowly progressive amyotrophic lateral

sclerosis, 3 being of the complete, or Charcot, type and the remaining 8 of the incomplete type. Four additional cases classified as of the Charcot type, another as of the atypical (monoplegic) type and, finally, another as of the incomplete type (progressive muscular atrophy with fibrillations) can, it would seem, be added to these 11 cases. The progress of the disease in the last 6 cases was arrested, was very slowly progressive or, as in 1 case, was arrested and followed by improvement. All of the patients are still alive and have been ill for from five to eleven years.

More recently 3 similar cases have been observed at the Long Island Hospital, Boston. In 2 cases the condition was characterized by amyotrophy of about twenty-five years' duration. In 1 of these the muscular atrophy had developed rapidly over a period of two or three years and had since remained stationary. The patient had serologic evidence of syphilis.³⁸ In the second case the amyotrophy had been very slowly, but steadily, progressive, and bulbar amyotrophy had developed during the last six months. In the third case advanced amyotrophy, bulbar palsy and lateral sclerosis of eight years' duration were exhibited. Little progress had been noted in the patient's condition for several years, and recently she had gained in strength.

Thus, a total of 20 patients might be considered to have slowly progressive or arrested amyotrophic lateral sclerosis, 8 of them exhibiting signs of pyramidal tract disease plus amyotrophy, the remaining 12 manifesting only amyotrophy. Some of these patients noted that the disease had been rapidly progressive in the beginning, at which time others noted muscular twitchings. In the remaining patients the disease had been slowly and steadily progressive from the start. The problem at hand is to determine how frequently the course of the disease may be so prolonged. According to the present study, this may occur in at least 5 per cent, and in no more than 10 to 15 per cent of cases. Perhaps these have caused the controversy in connection with vitamin E therapy. Also, one must not overlook the influence of incidental conditions, such as cardiac failure and chronic sepsis, on neurologic conditions in general, and more specifically on amyotrophic lateral sclerosis. Their relief through specific and general therapies undoubtedly benefits the underlying condition.

If amyotrophic lateral sclerosis can become arrested, it seems reasonable to expect that very slowly progressive muscular atrophy can suddenly become rapidly progressive. This appears to have happened

38. It is quite likely that this patient's amyotrophy was due to syphilitic lesions in the spinal cord. This cause must be very uncommon, however, since only 1 case in the present series had serologic evidence of syphilis, and a past history of syphilis was almost as rare—a check revealing no past history of syphilis in 50 of the most recent cases.

in 1 case, in which for five or six years the amyotrophy had been very slowly progressive and without fascicular twitchings. Rather suddenly fibrillations developed in the shoulder girdles, and when the patient entered the hospital knee and ankle jerks were hyperactive and a Babinski sign was elicited on one occasion. In less than two years he died.

Problems of classification cannot be decided arbitrarily, especially since there are so few pathologic and no physiologic or biochemical data. Possibly all patients with amyotrophic lateral sclerosis die of the disease according to schedule, and the arrested or slowly progressive forms represent an entirely different condition. This concept is held by many investigators of the problem. Diagnosis, based on the latter concept, will many times be difficult because the forms of the disease are not demarcated into distinct groups but, rather, merge with one another. This spectral relationship was brought out in the large number of cases studied, and is represented schematically in the figure. Neither concept of the relationship of these conditions should lead to needless confusion in judging the efficiency of therapy if one recognizes that the course of the disease may be variable.

Examples of slowly progressive muscular atrophy have been described before, notably in the English literature by Dreschfeld³⁹ and Dana.⁷ Both these authors reviewed the older literature and pointed out the apparent lack of familiarity of American and English writers with the condition. The relationship of syphilis in these cases is not at all clear. None of the cases in this series were complicated by this condition, whereas earlier writers expressed the belief that in most of their cases the disease was caused by syphilis. Amyotrophy due to syphilis is quite distinctive pathologically,⁴⁰ but conceivably could be confused with nonsyphilitic amyotrophy, especially if the blood and spinal fluid were not examined serologically.

The relationship of primary lateral sclerosis to amyotrophic lateral sclerosis is subject to the same dual interpretation; namely, the two conditions may be closely related, one being more slowly progressive than the other (figure), or they may be distinct and separate entities. It suffices to point out here that the clinical findings referable to the pyramidal tracts were the same in both instances, except that urgency of urination was infrequent in cases of slowly progressive primary lateral sclerosis and that in 6 of 8 clinical cases of primary lateral sclerosis pathologic studies showed degenerating ventral horn neurons.⁹ It is

39. Dreschfeld, J.: On Some of the Rarer Forms of Muscular Atrophies, *Brain* 8:164-190, 1885.

40. Martin, J. P.: Amyotrophic Meningo-Myelitis (Spinal Progressive Muscular Atrophy of Syphilitic Origin), *Brain* 48:153-182, 1925. Putnam, T. J., and Alexander, L.: Tissue Damage Resulting from Disease of Cerebral Blood Vessels, *A. Research Nerv. & Ment. Dis., Proc.* (1937) 18:544-567, 1938.

noteworthy that the signs referable to the pyramidal tract in cases of posterolateral sclerosis³⁰ may also be similar to those which were observed in cases both of amyotrophic lateral sclerosis and of primary lateral sclerosis, and that amyotrophy may develop in cases of posterolateral sclerosis.⁴¹

Recent pathologic studies have contributed to a better understanding of the fundamental lesions in amyotrophic lateral sclerosis. In a study of the brains and spinal cords from 37 patients with this condition, Davison⁴² found the pyramidal tracts in the spinal cord degenerating in all cases, in the medulla as well in all but 4 cases, in the pons and medulla as well in all but 16 cases and in the peduncles, pons and medulla as well in all but 23 cases. In only 12 cases could degeneration be traced from the large pyramidal cells in the frontal cortex into the brain stem and spinal cord. Moreover, the pathologic changes in the spinal cord and lower portion of the brain stem were old and were characterized by gliosis and the complete absence of many nerve fibers, whereas in the upper part of the brain stem the lesions were younger and were characterized by absence of gliosis and by the presence of fragmenting nerve fibers, easily identified in Marchi and sudan III preparations. Davison concluded that the upper motor neuron may begin to degenerate anywhere along its course, but chiefly in the brain stem and spinal cord. He pointed out that these general observations were noted some years ago, but had apparently been forgotten.

Davison's observations do not support the widely held belief that in amyotrophic lateral sclerosis degeneration starts in the motor cortex and proceeds down the pyramidal tracts. On the contrary, they suggest that degeneration begins in the most caudal part of the pyramidal tract and proceeds centralward, so that only in the most severe cases is the entire tract involved, and then much less in the upper than in the lower part of the brain stem. The clinical findings in the present study are in accord with such a concept, inasmuch as the signs of pyramidal tract disease appeared first in the legs and later in higher levels.

Pathologic studies in clinical instances of primary lateral sclerosis by Spiller⁹ and in cases of posterolateral sclerosis by Russell, Batten and Collier⁴³ revealed similar changes in the pyramidal tracts. In addition to lesions in the pyramidal tracts, degeneration has also been noted

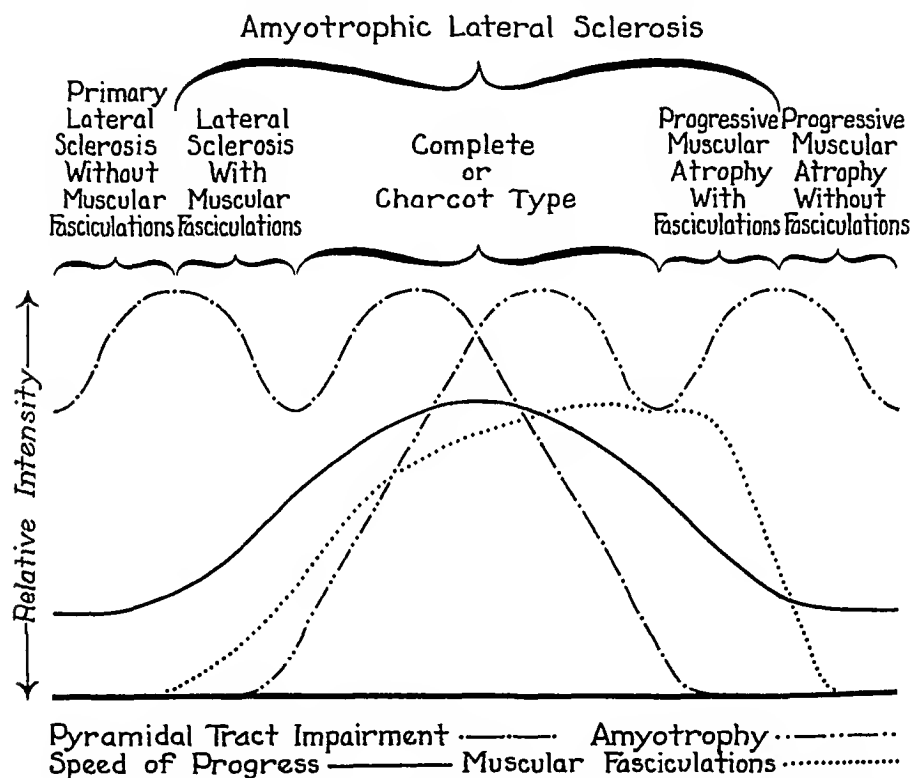
41. Hassin, G. B.: Amyotrophic Lateral Sclerosis Complicated by Subacute Combined Degeneration of Cord: Clinical and Pathologic Report of Case, *Arch. Neurol. & Psychiat.* **29**:125-138 (Jan.) 1933.

42. Davison, C.: Amyotrophic Lateral Sclerosis: Origin and Extent of the Upper Motor Neuron Lesion, *Arch. Neurol. & Psychiat.* **46**:1039 (Dec.) 1941.

43. Russell, J. S. R.; Batten, F. E., and Collier, J.: Subacute Combined Degeneration of the Spinal Cord, *Brain* **23**:39-110. 1900.

in the rubrospinal,⁴⁴ spinocerebellar⁴² and spinothalamic⁴² tracts in cases of amyotrophic lateral sclerosis, the relative infrequency of the spinothalamic changes suggesting that they develop later. It is quite possible that the subjective and later objective sensory alterations in a few of these cases are due to degeneration of the spinothalamic tracts.

By means of fiber analysis, Wohlfart and Swank^{10c} demonstrated that large nerve fibers in the ventral spinal roots degenerated first in cases of amyotrophic lateral sclerosis, leaving the small fibers relatively intact. The large ventral horn nerve cells suffered a similar fate, the



Schematic representation of the spectral relationship of the clinical features of the conditions analyzed in this study. Note the reciprocal relationship of amyotrophy and evidences of impairment of the pyramidal tract. Note, also, the close correlation of muscular fibrillations and the speed of progress of the disease.

small cells remaining relatively unharmed. The large fibers in the corticospinal tract areas of the spinal cord also appeared to suffer most in this condition, but accurate measurements of these fibers were impossible, owing to the presence of glial tissue. The inference from this study is that an orderly sequence of degeneration, based on fiber size, occurs in the ventral roots and corticospinal tracts in cases of amyotrophic lateral sclerosis.

44. (a) Kuré, K.: Die vierfache Muskelinnervation, Berlin, Urban & Schwarzenberg, 1931. (b) Wohlfart and Swank.^{10c}

sclerosis; the large fibers degenerate first, and progressively smaller fibers degenerate subsequently. Similar suggestions were made previous to this by Kuré^{44a} and Hechst,⁴⁵ but their observations were limited and were not supported by measurements.

The observations of Grund⁴⁶ and Shelden and Woltman⁴⁷ indicate that, contrary to prevailing opinion, the impulses which provoke fascicular twitchings in patients with amyotrophic lateral sclerosis may arise outside the cell body. These investigators blocked the nerve supply of fibrillating muscles with procaine at a point near the spinal cord and observed that the fibrillations continued even though the muscle was completely paralyzed. Further investigation along this line^{47a} has corroborated these observations and has shown in addition that injection into a nerve trunk near the muscle it supplies may stop or diminish the fibrillations in most instances, but that sometimes it is necessary to inject procaine directly into the muscle to stop them entirely. These studies suggest that the impulses causing fasciculations arise in the nerve near the muscle, or possibly in the muscle itself in some cases, rather than in the cell body. Furthermore, it suggests that the degenerative changes in the peripheral motor nerves are appearing first in the distal part of the nerve fiber, and not in the cell body. The observation of Denny-Brown and Pennybacker⁴⁸ that fasciculations continue in antagonistic muscles during voluntary movement does not appear to conflict with this conception.

Degeneration, according to this pattern, has been shown to occur in cases of thiamine deficiency by Swank⁴⁸ and Swank and Prados.⁴⁹ In this condition degeneration usually first appears in the distal part of a neuronal process and subsequently progresses toward the cell body. The cell body exhibits the axon reaction later, or in many instances not at all. It is of considerable interest that large fibers degenerate first both in thiamine deficiency and in amyotrophic lateral sclerosis, but in the former condition the proprioceptive sensory fibers are affected first, and in the latter, the large motor nerve fibers. In alcoholic patients it has also been

45. Hechst, B.: Zur Pathohistologie und Pathogenese der amyotrophischen Lateralsklerose, *Arch. f. Psychiat.* **93**:159-181, 1931.

46. Grund, G.: Ueber die Entstehung der fibrillären Muskelzuckungen bei spinalen Amyotrophien, *Deutsche Ztschr. f. Nervenhe.* **145**:99-109, 1938.

47. Shelden, C. H., and Woltman, H. W.: Origin of Fibrillary Twitchings, *Proc. Staff Meet., Mayo Clin.* **15**:646-648, 1940.

47a. Work in progress, with the collaboration of Dr. J. C. Price, of the Neurological Institute of New York.

48. Swank, R. L.: Avian Thiamin Deficiency: Correlation of Pathology and Clinical Behavior, *J. Exper. Med.* **71**:683-702, 1940.

49. Swank, R. L., and Prados, M.: Avian Thiamin Deficiency: II. Pathological Changes in the Brain and Cranial Nerves (Especially the Vestibular) and Their Relationship to the Clinical Behavior, *Arch. Neurol. & Psychiat.* **47**:97-131 (Jan.) 1942.

shown by Greenfield and Carmichael⁵⁰ that the large nerve fibers in the peripheral nerves suffer the greatest damage. These facts suggest that in some fundamental way the metabolism of motor neurons differs from that of sensory neurons.

It was indicated earlier in this paper that therapy of amyotrophic lateral sclerosis with vitamin E or vitamin B₆ had not been wholly satisfactory. A possible explanation for a few of the optimistic reports has already been offered, namely, that in a few untreated patients the course of the disease is prolonged. All other methods of treatment, to date, have been equally ineffective in altering the course of this disease, with several possible exceptions. Patients with marked bulbar palsy may be greatly improved, although only temporarily, by tube feeding. This improves the general condition of the patient and lessens the incidence of aspiration pneumonia. Also, patients with coincidental cardiac failure, chronic sepsis and similar maladies are frequently greatly benefited by improvement in these superimposed burdens. The hope that amyotrophic lateral sclerosis will respond to specific therapy should not be abandoned, however, in view of the irregular course of the disease in some cases.

SUMMARY

The records of 197 patients with amyotrophic lateral sclerosis, primary lateral sclerosis or progressive muscular atrophy (various types) are analyzed and classified on the basis of their chief clinical manifestations, namely, lateral sclerosis, amyotrophy and muscular fascicular twitchings.

The cases of amyotrophic lateral sclerosis were broken down into three chief types: the Charcot, or completely developed; the atypical, and the incompletely developed. The large majority of the cases were of the first type. They were the typical cases and were characterized by well developed amyotrophy, muscular fasciculations and pyramidal tract signs. The second, or atypical, type included the so-called monoplegic, hemiplegic, lumbar and proximal forms. Each of these terms refers primarily to the distribution of the amyotrophy, degeneration of the pyramidal tracts being essentially the same in all. In most of the cases of the atypical type the amyotrophy eventually developed in other extremities and the clinical picture became complete.

The cases of incompletely developed amyotrophic lateral sclerosis were characterized by predominance of lateral sclerosis, amyotrophy or bulbar palsy. The patients with lateral sclerosis presented rapidly developing pyramidal tract disease with urgency of urination and muscular fibrillations (but no atrophy). The patients with amyotrophy alone pre-

50. Greenfield, J. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of Cord, Brain 58:483-491, 1935.

sented rapidly developing muscular atrophy with many muscular fibrillations, and the patients with bulbar palsy showed little besides the bulbar amyotrophy.

In cases of amyotrophic lateral sclerosis there appeared to be a close correlation of the number of muscular fibrillations and the speed of progress of the disease. It should be remembered, however, that the fibrillations may vary from time to time. Elevation of the cerebrospinal fluid proteins seemed to accompany severe amyotrophy, but did not necessarily indicate its rapid progression. Urgency of urination reflected rapid advancement of the pyramidal tract involvement.

Degeneration of the pyramidal tracts was indicated first by hyperreflexia in the legs and later in the arms, then by a Babinski sign and, finally, by absence of abdominal reflexes. Bulbar involvement was usually indicated by amyotrophy first of the muscles supplied by the twelfth cranial nerve, then of the muscles supplied by the ninth and tenth nerves and the lower part of the seventh nerve, and, finally, of the muscles innervated by the masticator division of the fifth nerve. Pains of varying character were common and were often an early symptom, but objective sensory changes were rarely observed.

Primary lateral sclerosis and progressive muscular atrophy, both without muscular fibrillations, ran a course similar in many ways to that of amyotrophic lateral sclerosis, except that it was more slowly progressive. It is suggested that the patients with slowly progressive muscular atrophy without muscular fasciculations were suffering from an arrested or a slowly progressive type of amyotrophic lateral sclerosis, approximately 10 per cent of the cases falling into this group. The reasons for and against this concept are presented, but the absence of suitable pathologic data precludes settlement of the problem at present. Data are also presented which suggest that an occasional patient with the clinical picture of amyotrophic lateral sclerosis recovers.

Miss Sadie Shapiro, of the Social Service Department of the Neurological Institute of New York, assisted in following up patients after discharge.

Fifth General Hospital, United States Army, A. P. O. 1001, % Postmaster, New York.

700 West One Hundred Sixty-Eighth Street.

HISTOGENESIS OF THE EARLY LESIONS OF MULTIPLE SCLEROSIS

I. SIGNIFICANCE OF VASCULAR CHANGES

I. MARK SCHEINKER, M.D.

CINCINNATI

Putnam and his co-workers¹ were the first to assign a primary role to vascular lesions in the pathogenesis of multiple sclerosis. They succeeded in producing patches of demyelination by the intravenous injection of various substances (e. g., tetanus toxin). The likeness of such lesions to the foci of multiple sclerosis indicated the possibility that the lesions of multiple sclerosis might be produced by a local circulatory disturbance, "apparently of the nature of an obstruction on the venous side." Dow and Berglund² analyzed a large number of lesions of multiple sclerosis. They found thrombi only fifteen times in sixty-five blocks carefully examined. Marburg³ observed that "thrombosis occurs in acute foci of multiple sclerosis more frequently than is generally assumed. . . . Yet, there are many foci in which blood vessels exhibit no changes in their walls and no venous obstruction."^{3b}

The object of this paper is to present additional evidence in support of the primary role of vascular lesions in disseminated sclerosis. The majority of investigators have described the condition of the vessels in multiple sclerosis. Most attention has been given to older plaques, which must be considered as glial scar formations. It is worth while

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

1. (a) Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, *J. A. M. A.* **97**:1591-1596 (Nov. 28) 1931. (b) Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, *New England J. Med.* **209**:786-790, 1933; (c) Evidence of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," *Arch. Neurol. & Psychiat.* **37**:1298-1321 (June) 1937. (d) Alexander, L., and Putnam, T. J.: Cerebral Lesions Due to Vascular Occlusion, *ibid.*, to be published.

2. Dow, R., and Berglund, G.: Vascular Pattern of Lesions of Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **47**:1-18 (Jan.) 1942.

3. Marburg, O.: (a) Die sogenannte akute multiple Sklerose (Encephalomyelitis periaxialis scleroticans), *Jahrb. f. Psychiat.* **27**:213-312, 1906; (b) Studies in the Pathology and Pathogenesis of Multiple Sclerosis with Special Reference to Phlebothrombosis and Guiraud's Bodies, *J. Neuropath. & Exper. Neurol.* **1**: 3-13 (Jan.) 1942.

to emphasize that in these old lesions the tissue has become secondarily changed. On that account they will receive only passing mention here. A study of the first stages of plaque formation would appear to be of greater significance.

MATERIAL AND METHOD

Twenty cases of multiple sclerosis were studied at the neuropathologic laboratory of the Salpêtrière.⁴ In 15 cases the whole brain and spinal cord were available; in 5 cases the histologic study was limited to the brain. All cases studied were typical examples of multiple sclerosis from the clinical and pathologic points of view. Histologic examination by the Spielmeyer, Bielschowsky and Holzer methods confirmed in every instance the clinical diagnosis of multiple sclerosis.

For the present study care was taken to reconstruct a picture of the first stages of plaque formation. In order to be able to trace the process from the beginning the histologic analysis was limited to lesions which were not visible to the naked eye. To obtain this material all gross lesions were avoided and sections were prepared from grossly intact areas. The centrum semiovale, boundaries between the cortex and the white matter and the periventricular areas served as fixed points. Sections were stained by the Spielmeyer, Bielschowsky, Holzer, Cajal, Hortega, scarlet red and hematoxylin and eosin technics. For the demonstration of vascular changes Mallory's connective tissue stain and phosphotungstic acid hematoxylin were used.

RESULTS

Changes in the Myelin Sheaths.—In all cases the loss of myelin was the cardinal feature of the histologic picture. There was an enormous variety in size, shape, demarcation and number of the demyelinated plaques. The usual type described in most textbooks as a more or less sharply circumscribed lesion entirely devoid of myelin was not observed frequently in my material. Such lesions existed in these cases, but they were common only among the older and larger plaques. Their analysis and description are of no interest for the present purpose and are therefore omitted. In many cases areas of demyelination were observed in which the myelin was only partially altered. These areas represented the so-called myelin shadow plaques (Spielmeyer, Steiner) and were distinguished from the completely demyelinated lesions by (a) their dark gray color, (b) the preservation of numerous beaded and thin myelin sheaths, (c) their irregular margins, imperceptibly fading out into the surrounding normal tissue, and (d) their relatively small content of lipid products (scarlet red).

The majority of the small areas of demyelination were perivascular. Their relation to the vascular system is illustrated in figure 1 *A* and *B*. Under low magnification these areas of perivascular demyelination

4. Professor Guillain and Dr. Ivan Bertrand gave me permission to use this material.

appeared as light-staining circular or oval zones surrounding small veins and capillaries. Each lesion contained a blood vessel, which was usually so oriented as to be central. In the majority of the lesions the central vessel could be identified as a small vein. The perivascular areas of demyelination revealed the following characteristic changes in the myelin sheaths: In the central part of the plaque the destruction of myelin was generally complete, practically no or very few fragments being discernible (fig. 1 *A*). At the periphery a transitional zone was often observed, characterized by swelling, fragmentation and beading of the myelin sheaths. This zone, however, was sometimes very small or imperceptible, so that the transition between destroyed and normal myelin was rather abrupt, the demyelinated lesions being sharply defined. As a rule an

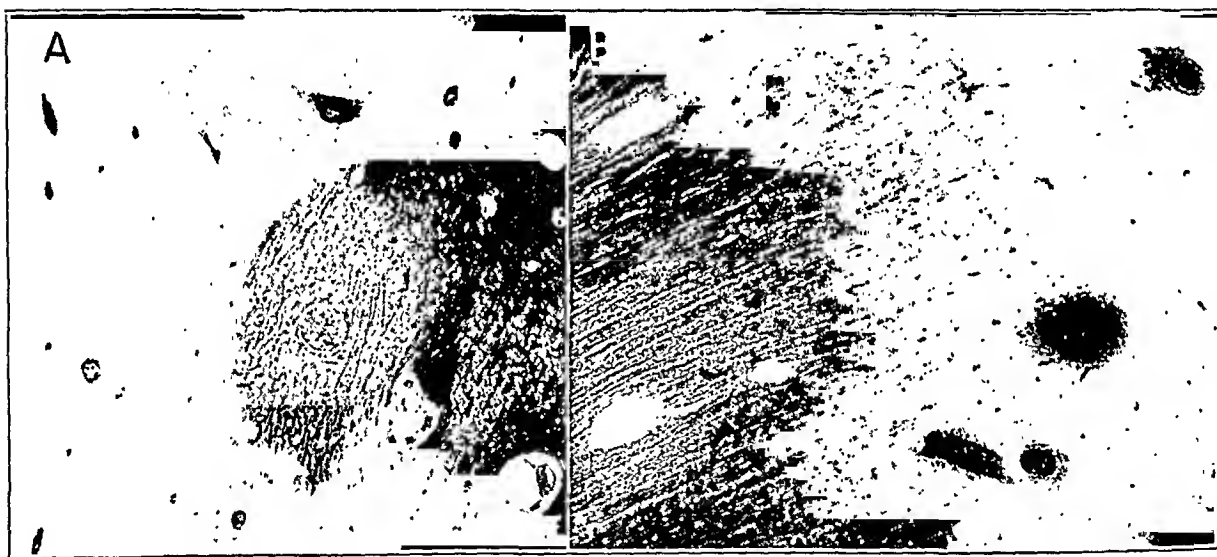


Fig. 1.—*A*, an “early” perivascular plaque about an obstructed blood vessel; $\times 80$. *B*, circular or oval zones of demyelination surrounding small blood vessels; $\times 70$. Spielmeyer myelin sheath stain.

intermediate zone lay between the necrotic center and the marginal portion of the lesion, in which the myelin sheaths stained lightly and were often thin and beaded.

Changes in the Axis-Cylinders.—Spielmeyer and Bielschowsky preparations were made of adjacent sections from the same block of tissue. In general it appeared that all plaques could be divided in three types: (1) those in which the axis-cylinders were completely destroyed and practically absent; (2) those in which the axis-cylinders were severely damaged and reduced in number, and, finally, (3) those in which the axis-cylinders were fairly well preserved or substantially intact. It appeared that the last type of lesion was the most common among the

small perivascular patches. In some of the plaques no definite diminution in number of axis-cylinders could be observed. Sometimes, however, in the center the axis-cylinders were fragmented and degenerated and slightly decreased in number, whereas in the periphery they appeared to be substantially intact. In general, it can be said that the destruction was less noticeable as one passed from the center to the periphery of the lesion. In many of the smallest perivascular plaques there was extreme tumefaction of the axis-cylinders. Presumably this axonal swelling represents one of the earliest changes, and one which may be reversible.

Changes in the Glia.—In the majority of descriptions of the histologic changes in multiple sclerosis the early glial changes have not been stressed. They may, therefore, be described in detail. Three types of glial reaction were observed. There was pronounced rarefaction and a spongy appearance of the glial reticulum, with loss of affinity for the stain. In many small plaques the tissue contained numerous vacuoles, some of which harbored myelophages and gitter cells. Many of the plaques were traversed by preexistent glia fibers, which in some instances were torn by the distended vacuoles. Similar changes were first described by Redlich⁵ as a predominant feature of early plaque formation. Borst⁶ interpreted these changes as due to lymph stagnation (so-called *Hyperlymphose*). Steiner⁷ described them as *circumfocale Areolierung* and observed this type of glial change mostly in the tissues surrounding the plaques. In Cajal and Holzer preparations the neuroglia appeared degenerated in the central part of the lesion. At the periphery some degenerated astrocytes could be seen; their cytoplasm was swollen and their dendrites were broken. In some lesions there was a slight increase of connective tissue, seemingly originating from the blood vessel walls.

In some of the patches Hortega preparations revealed numerous microglia cells with the most bizarre nuclei, most of which were bean shaped or kidney shaped. At the periphery of the foci various phases of transformation of the microglia into compound granular cells could be observed. Some of the patches contained numerous gitter cells, which were associated with occasional gemästete cells and with many myelophages. Astrocytes were rarely observed and were usually present only in the marginal areas of the patches. In some regions gemästete cells attained enormous dimensions and appeared as monster cells.

Glial fibrosis in the form of scars was only occasionally observed. In such areas in which the glial reaction was especially active prolifera-

5. Redlich, E.: Ueber multiple Sclerosis, *Deutsche Klin.* 6:557-587, 1906.

6. Borst: Die multiple sklerose des Zentralnervensystems, *Ergebn. d. allg. Path. u. path. Anat.* 9:67-187, 1903-1904.

7. Steiner, G.: Krankheitserreger und Gewebefund bei multipler Sklerose, Berlin, Julius Springer, 1931.

tion of astrocytes was conspicuous. Comparison of this type of glial reaction with that described in older lesions showed no structural differences. A more detailed description of them is therefore omitted.

Vascular Changes.—The relation of the vascular system to the lesions has been mentioned and is illustrated in figure 1. In about two thirds of all early lesions stained by the Spielmeyer method, the patches were in the form of circular or oval demyelinated plaques which surrounded medium-sized veins or capillaries. Most of the blood vessels within the

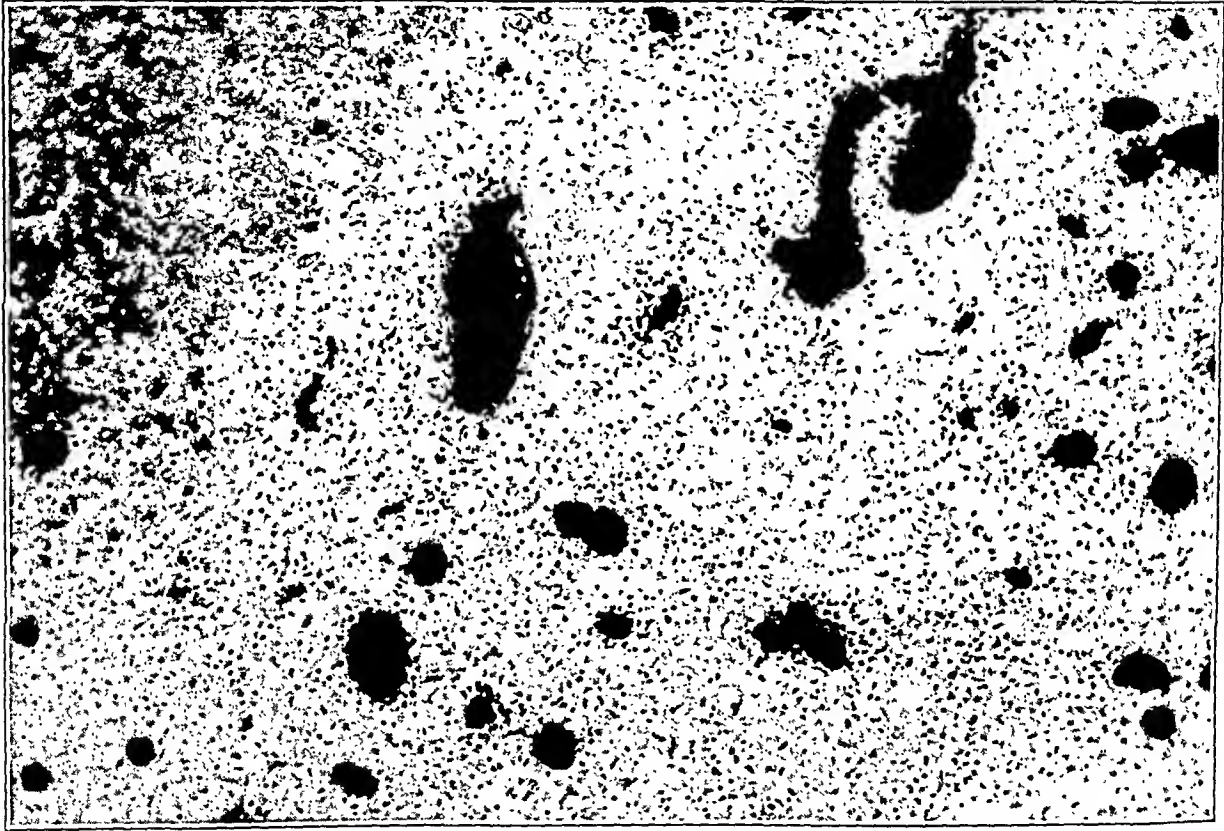


Fig. 2.—Marked dilatation, engorgement and stasis of the small blood vessels in a demyelinated area. Spielmeyer myelin sheath stain; $\times 110$.

lesions revealed marked dilatation and enormous engorgement with blood (fig. 1 *A*). In some of the larger lesions the vascular engorgement and stasis were especially striking (figs. 2 and 3 *A* and *B*). The small veins and capillaries were enormously distended and showed some tortuosity and beadlike dilatations.

The presence of vascular occlusion and thrombus formation was not always easy to identify. Clots of agglutinated red blood cells were frequently observed. The individual red blood cells were usually fused

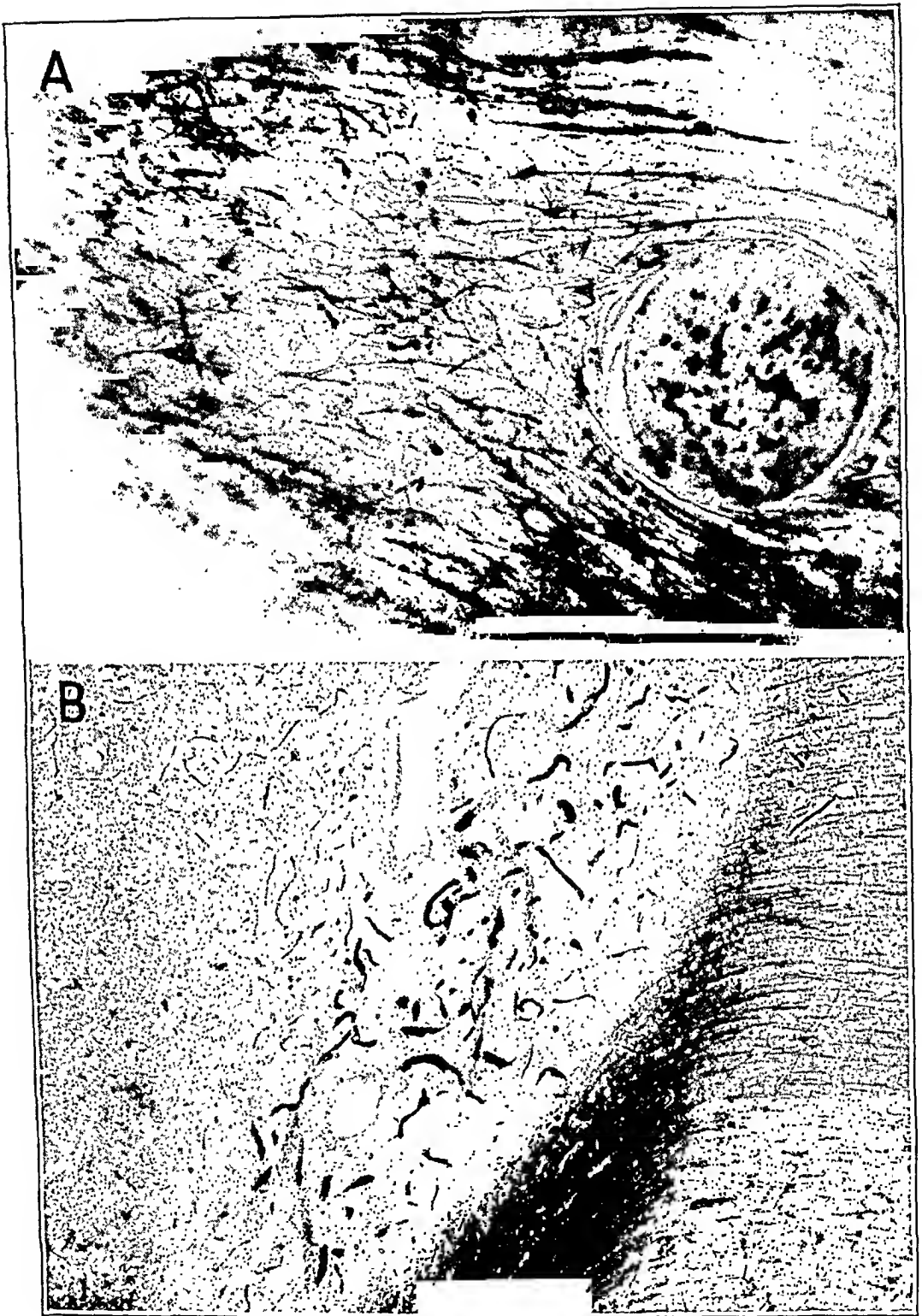


Fig. 3.—*A*, perivascular loss of myelin sheaths; complete filling of the central blood vessel with agglutinated platelets, fibrin and pigment. $\times 125$. *B*, vascular engorgement and stasis of the small blood vessels in a larger area of demyelination. $\times 125$. Spielmeier myelin sheath stain.

together and formed an amorphous mass. In some areas the occlusive changes consisted of complete filling of the vascular channel with large masses of agglutinated platelets, broken-down blood corpuscles and a few strands of freshly formed fibrin and pigment (fig. 3 *A*). More striking occlusive changes are illustrated in figure 4 *A*. They consisted of complete filling of the lumen of the blood vessel by a solid plug of agglutinated blood mixed with an unusually heavy deposit of strands of fibrin curved toward the vessel wall. Occasionally an early stage of organization was associated with degenerative changes of the vessel wall (fig. 4 *B*). In addition to these vascular changes, perivascular hemor-

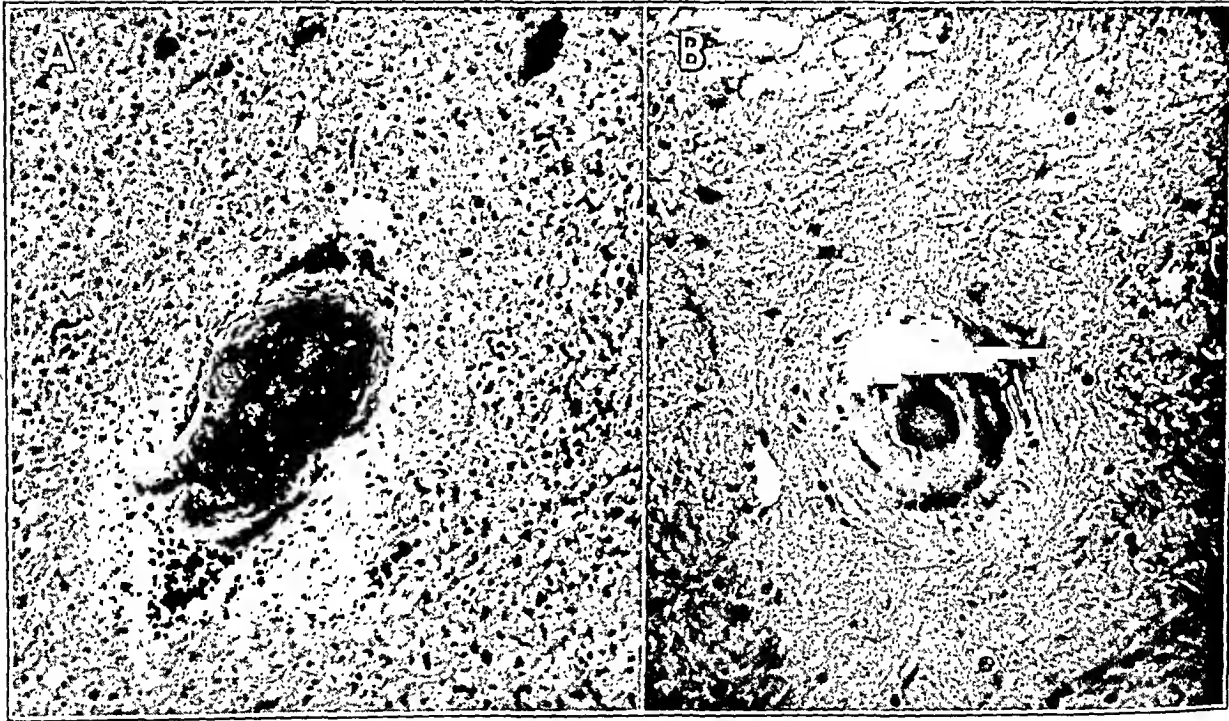


Fig. 4.—*A*, completely occluded blood vessel in the central area of a demyelinated plaque, showing solid plug of agglutinated blood mixed with strands of fibrin adherent to the wall of the vessel. *B*, a blood vessel in the vicinity of a plaque completely occluded by a partly organized thrombus. Hematoxylin and Van Gieson stain; $\times 135$.

rhages and deposits of yellow pigment were often observed in the distended perivascular spaces.

Perivascular Infiltration and Inflammatory Phenomena.—In about one third of the cases perivascular accumulation of cells was observed. In some cases the majority of the perivascular cells could be identified as fat granule bodies. Others were rod cells. Further, proliferation of astrocytes within the perivascular tissue was fairly constant. Accumula-

tions of lymphocytes were seldom observed. There was a marked variation in the content of lymphocytic infiltration not only from case to case but from lesion to lesion in the same case. In general, it appeared in this series of cases that lymphocytic infiltration was an infrequent occurrence.

COMMENT

This study has demonstrated rather strikingly the frequent association of the early lesions of multiple sclerosis and vascular disturbances. The latter consisted of thrombosis of small veins and dilatation, engorgement and stasis of the capillaries and veins. The great majority of small lesions have been observed to be oriented about small veins. The question inevitably arises why vascular disturbances, which can be considered as of frequent occurrence in small and recent plaques, are relatively infrequent in the large and older lesions.

Two factors appear to be of importance: 1. In elongated lesions containing central veins the patches never tend to follow the entire course of the blood vessel.⁸ In the great majority of instances only one circumscribed area of the plaque is connected with the blood vessel. The foci usually envelop the central vein for a short and limited distance. As the lesion becomes larger the relation with the primary blood vessel becomes less evident. The demyelinated area tends to progress diffusely into the nerve parenchyma in different directions independent of the distribution of the primary blood vessel. It is not surprising, therefore, that in many sections from a large lesion the primary blood vessel will not be found. 2. The presence or absence of vascular changes in lesions may depend on the duration of the morbid process. Alexander and Putnam^{1a} suggested that thrombi of the small veins in the older lesions of multiple sclerosis may disappear without a trace. Certainly, in older sclerotic plaques it is more difficult to trace them than in the recent lesions.

SUMMARY

In 20 cases of multiple sclerosis the early stages of plaque formation and their relation to the vascular system were studied. A positive correlation was found between the early lesion and the presence of vascular abnormality. The view is expressed that vascular change, particularly occlusion by thrombosis, is an essential factor in the pathogenesis of demyelinated plaques.

Cincinnati General Hospital.

8. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **38**:1-15 (July) 1937.

EFFECT ON THE ELECTROENCEPHALOGRAM OF CHANGING THE BLOOD SUGAR LEVEL

PAULINE A. DAVIS, M.A.†

CAMBRIDGE, MASS.

In 1939-1940 electroencephalographic observations and determinations of the blood sugar were made on a group of 43 college undergraduates under standardized conditions. An attempt was made to relate the range of blood sugar levels to the type of the electroencephalographic pattern (Davis¹), the alpha frequency and the normality rating of the electroencephalogram. No correlation was found. An attempt was also made to relate the electroencephalographic pattern to the responses of the electroencephalogram during three minutes of hyperventilation. The low voltage, fast frequency types of electroencephalograms (beta or mixed fast patterns¹) appeared to be more resistant to change than the alpha or mixed slow types. Aside from this, there were no consistent observations. It appears that the fasting blood sugar level of a subject has no consistent relation to the electroencephalogram.

In 1940-1941 electroencephalographic observations were made on 40 healthy college students simultaneously with an "insulin tolerance test."² The study of the electroencephalographic pattern with a varying blood sugar level is the basis of the present paper.

METHOD

A routine electroencephalogram was recorded for one-half hour between 8 and 9 a. m., while the subject was in a fasting condition; i. e., he had not had food for the previous twelve hours. The routine electroencephalogram included simultaneous records from both sides of the head and the midline of the frontal, the precentral and the occipital region.¹ If asymmetry between the two sides of the head was found, the more normal side was chosen for continuous recording later in the procedure. Insulin (0.05 unit per kilogram of body weight of insulin

† Mrs. Davis died on July 11, 1942.

This work was aided by a grant from the Josiah Macy Jr. Foundation. Through the Grant Study of Harvard University, Dr. Clark Heath and Dr. John Thompson collaborated in the blood sugar determinations.

1. Davis, P. A.: *Technique and Evaluation of the Electroencephalogram*, J. Neurophysiol. **4**:92, 1941.

2. Csépai, K., and Ernst, Z.: *Insulin Susceptibility of the Human Body*, Orvosi hetil. **71**:1497, 1927. de Takáts, G.; Fenn, G. K., and Trump, R. A.: *Splanchnic Nerve Section in Juvenile Diabetes*, Ann. Int. Med. **7**:1201, 1934. Bauer, J., and Mongino, J.: *Ueber den Schwellenwert des Insulins*, Ztschr. f. klin. Med. **121**:476, 1932.

containing 40 units per cubic centimeter) was then injected intravenously, and from this time for one hour a continuous electroencephalogram and record of the pulse rate were made while the subject was lying comfortably relaxed on a bed with his eyes closed. Between forty-five and fifty minutes after injection of the insulin, 50 cc. of Karo corn syrup (Red Label) in an approximately equal amount of water was given the subject by mouth. Blood, for measurements of the blood sugar,³ was taken from the finger at two, twenty, twenty-five, thirty, thirty-five and forty-five minutes after the injection of insulin and fifteen minutes after the corn syrup was given. Blood pressure readings were made at approximately five minute intervals. Between fifteen and twenty minutes after the corn syrup was given, when the blood sugar usually approximates its original level, the subject's response to hyperventilation for three minutes was recorded electroencephalographically.

RESULTS

Forty-three observations were carried out on 40 healthy college students, whose ages ranged from 17 to 23 years, with 3 subjects repeating the experiment under the same conditions.

TABLE 1.—*Range in Pulse Rates*

	Bents per Minute
Average pulse rate before injection of insulin.....	38-76
Highest pulse rate.....	64-100
Pulse rate at 45 minutes.....	52-83
Pulse rate 15 minutes after ingestion of Karo corn syrup, approximately 1 hour after insulin.....	51-76
Acceleration	3-42
Deceleration from peak to 45 minutes.....	0-39
Deceleration from peak to 1 hour.....	3-33
Change: Deceleration (27 observations).....	0-14
Acceleration (14 observations).....	0-16

Blood Sugar.—The fasting blood sugar level varied from 92 to 129 mg. per hundred cubic centimeters. The lowest level, which was reached usually between twenty-five and thirty minutes after injection of insulin, varied from 53 to 85 mg. per hundred cubic centimeters. The blood sugar approached the fasting level at forty-five minutes and reached or exceeded it fifteen minutes after the corn syrup had been taken (76 to 126 mg. per hundred cubic centimeters).

Pulse Rate.—Table 1 gives the range of the pulse rates for these subjects. Changes in pulse rate were not correlated with changes in the electroencephalogram. There was a notable variability of pulse rate before and after the blood sugar level changed. The most rapid change in pulse rate occurred during the first minute of hyperventilation, while the electroencephalogram was still stable.

Blood Pressure.—Changes in blood pressure occurred, but they could not be correlated with electroencephalographic changes.

3. Folin, O., and Malmros, H.: An Improved Form of Folin's Micro Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115, 1929.

Electroencephalogram.—The electroencephalogram showed a slight shift toward the slow end of the frequency spectrum and increasing instability as the blood sugar level decreased. The transition occurring in response to insulin started as early as ten minutes, but usually not

E.E.G. Changes with Fall in Blood Sugar

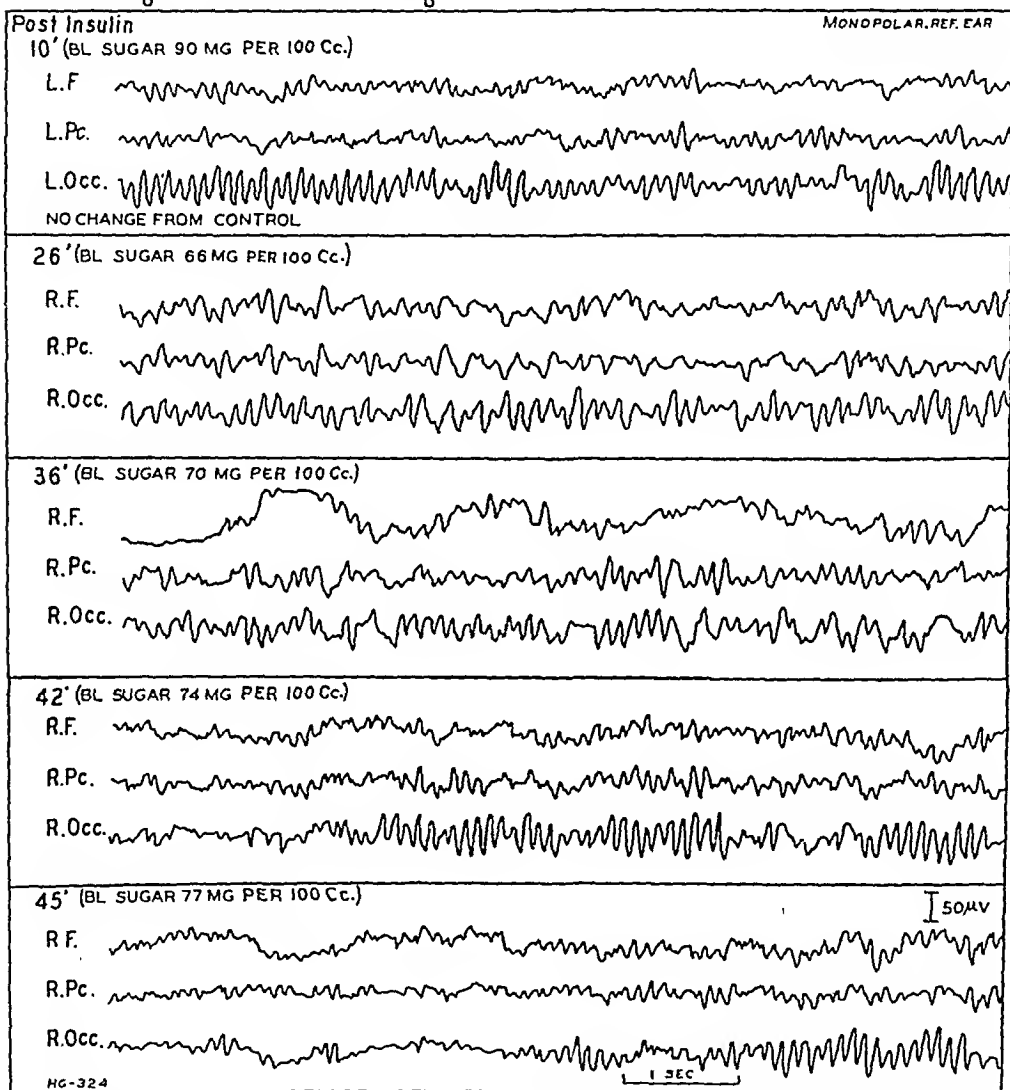


Fig. 1.—Typical electroencephalographic changes occurring with alterations in the level of blood sugar.

until twenty minutes after injection of the drug. The alpha activity became irregular and the per cent time alpha decreased as 8 per second or other slow waves appeared (fig. 1). The precentral record showed this change more clearly, although the base line of the simultaneous frontal record became unstable before the 8 per second waves were clearly developed.

From the thirtieth to the forty-fifth minute in most instances, long slow swings began emerging in the frontal record, usually obscuring the 4 to 8 per second activity (fig. 1). These slow swings were of from two to as long as five seconds' duration (fig. 2). Ultimately they gradually lengthened out until the base line became steady once more. Capacity-coupled amplifiers were employed, so that one could not be sure whether the stabilization was due to cessation of the slow swings or merely to their becoming so slow that they were no longer recorded by the amplifier. The consistency of the appearance of the slow swings made it possible to study their relationship to other factors. Although they

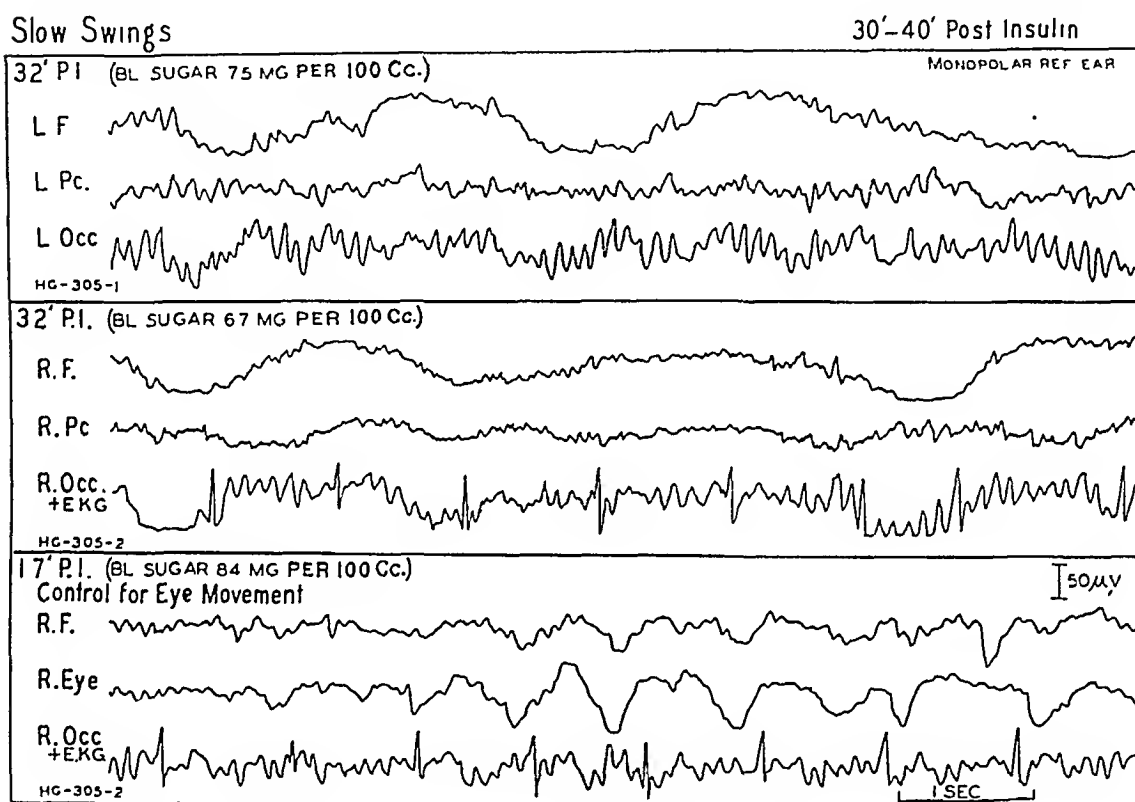


Fig. 2.—Slow swings occurring with alterations in the blood sugar level thirty to forty minutes after insulin and the control for eye movements. Eye movements, registered in the second line of the control sample, produced swings in the frontal record that were of less amplitude and much quicker than the "slow swings" shown in the first two samples. For recording of the pulse rate (second and third samples), one grid of the third amplifier was connected to a potentiometer placed between the electrode from the right ear and an electrode on the wrist. The other grid of this amplifier was connected to an occipital electrode, so that the occipital electroencephalogram and the electrocardiogram appear simultaneously in the record.

appeared most frequently from the frontal lead, they occasionally appeared from the occipital lead, while the record from the precentral lead was usually stable (fig. 2). These slow swings are similar to

those found by Lovell, Czarski and Lyman⁴ in experiments on the responses to stimulation of the vestibular mechanisms. These authors proved that the slow swings originated in the skin and were related to disturbances in the autonomic nervous system, as indicated by sweating, pallor and changes in respiration. It is worthy of note that these slow swings in the electroencephalographic record in the frontal and occasionally in the occipital region have been associated with disturbances of the autonomic nervous system, and yet that they have been produced by stimulation of the vestibular mechanisms and also by lowering the blood sugar level by means of injections of insulin. Probably in my subjects the autonomic nervous system was also involved, since the pulse rate generally increases as the blood sugar level reaches its minimum, and my subjects usually showed mild sweating and pallor.

By the forty-fifth minute these slow swings usually disappeared (fig. 1). In a few subjects hyperventilation caused reappearance of these swings for a short time. In 1 subject, who went into partial syncope seven minutes after injection of insulin, all three areas showed these swings. His blood pressure, which had been 104 mm. of mercury systolic and 74 mm. diastolic before insulin was given, fell to 75 mm. systolic and 45 mm. diastolic at the onset of the partial syncope and was 88 mm. systolic and 65 mm. diastolic three minutes later. Thereafter his blood pressure remained stable between 92 mm. systolic and 56 mm. diastolic and 104 mm. systolic and 60 mm. diastolic during the remainder of the experiment, while the long swings reappeared and remained from the twenty-fifth through the fifty-sixth minute. The experiment was repeated with this subject, but the swings did not appear. As electrodes were being put on before the second test, he volunteered the information that he had been inwardly a bit panicky and uncertain about what to expect in the first experiment.

In another subject, these swings appeared thirty-two minutes after injection of insulin in each of 2 experiments. The swings in the frontal record were found to be independent of the changes recorded from an eye lead placed just under and against the eyebrow (fig. 2). Administration of 100 per cent oxygen for approximately five minutes had no apparent effect on these swings.

The electroencephalogram usually remained unstable for from ten to twenty minutes after the level of blood sugar began to rise. The 4 to 8 per second waves became irregular as low voltage, 16 to 20 per second waves occasionally appeared. After this the electroencephalogram gradually resumed its previous character with the return of alpha activity

4. Lovell, H. W.; Czarski, T. J., and Lyman, R. S.: The Effect of Vestibular Stimulation on Brain Waves, *Chinese J. Physiol.* **14**:389, 1939.

(fig. 1). In all subjects the electroencephalogram was unstable when the lowest point in the blood sugar curve was reached. In some the irregular slow waves increased in voltage and developed into clear "episodes" (fig. 3), which continued to reappear even as long as twenty minutes after the administration of corn syrup.

Hyperventilation for three minutes was carried out after the blood sugar had returned to its normal level. A preliminary demonstration and explanation of hyperventilation were always given. The rate and depth of breathing for each subject were such that he could maintain

E.E.G. Changes relating to Blood Sugar

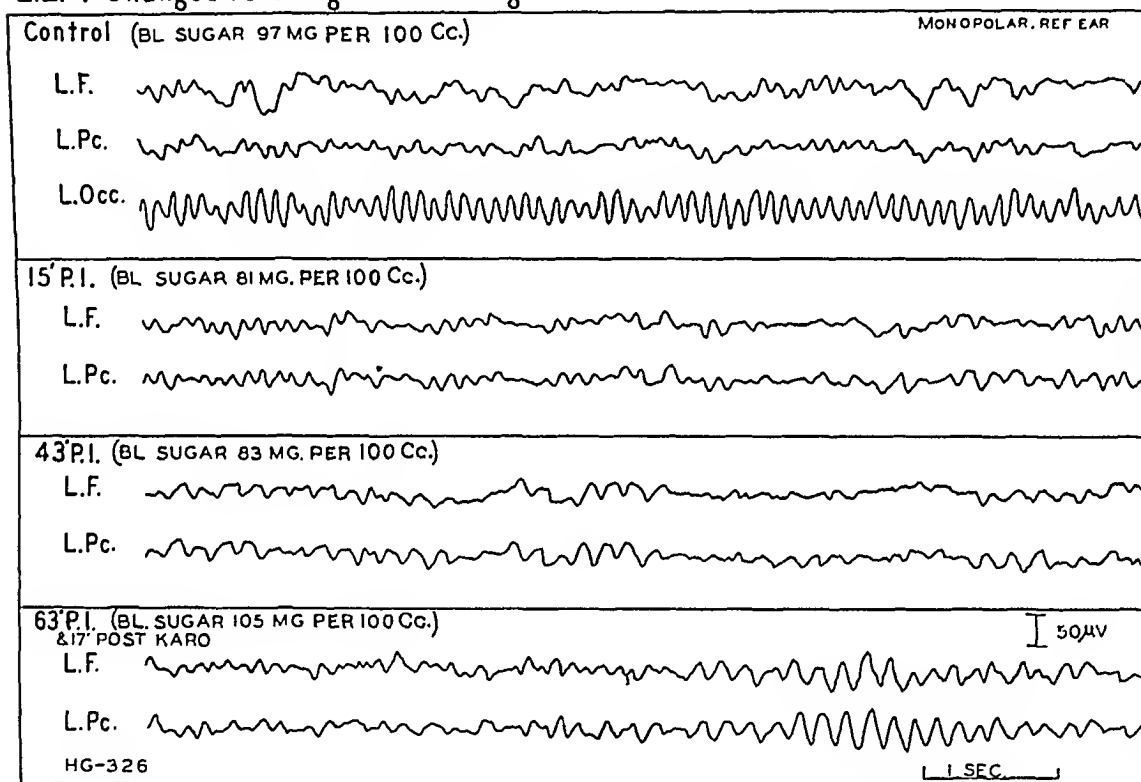


Fig. 3.—Organization of latent dysrhythmia into definite 6 cycle episodes as a result of altering the blood sugar level.

a steady pace at approximately his maximal capacity, with no delay between breaths. In this way an attempt was made to allow for individual differences in respiration by having the subject regulate his own breathing in meeting the requirements of the procedure.

The amount of alteration in the electroencephalogram following the injection of insulin and also on hyperventilation was rather clearly related to the character of the routine electroencephalogram. In general the subjects whose preinsulin records showed indications of slow dysrhythmic activity were the ones in whose records the most dysrhythmia appeared after insulin and the clearest "episodes" of slow waves developed. The records that were initially the most stable and regular,

or revealed faster than average alpha waves, and were freest from slow waves showed the least change after insulin or during hyperventilation.

All of the routine records were typed—alpha (*A*), beta (*B*), mixed fast (*MF*), mixed (*M*) and mixed slow (*MS*)—and rated for “nor-

TABLE 2.—*Classification of and Data on Electroencephalograms of Forty Healthy Subjects**

Electro- encephalo- gram No.	Relative Prominence of Slow Waves			Lowest Blood Sugar Level, Mg. per 100 Cc.	Type of Electro- encephalo- gram	Alpha Frequency	“Normality Rating”
	Routine	After Insulin	After Hyper- ventilation				
300	+++	+++	+++	76	M	10	4
303	+++	+++	+++	71	M	10.5	4
317	+++	+++	++	69	M	10+	4
325	+++	++	+	62	MS	8-10	4
306	++	+++	+++	59	MS	9	4
301	++	++	++	74	M	10	3+
324†	++	++	+	60	M	9.5-10	3+
338	++	++	—	77	M	10-11	4
343	++	++	—	76	B	11	3
311	++	—	++	65	M	10	3+
350	++	—	—	62	B	10-11	3+
326†	+	+++	+++	68	A	9-9.5	2+
302	+	+++	—	74	A	9-10	3+
272	+	++	++	53	A	9-10	3
275	+	++	+	57	MF	11	3
349	+	+	++	69	MS	9-10	3
347	+	+	—	81	MS	9.5-10	3+
348	+	+	—	70	B	10—	3
303†	+	+	—	72	A	10	3
346	+	+	—	67	MS	10	2+
342	+	—	+	85	MS	10	2+
341	—	++	—	77	MS	9.5-10	3+
310	—	+	—	62	M	11	2+
330	—	+	—	61	MF	11-12	2+
329	—	+	—	67	A	10	2+
315	—	—	++	62	M	10	3
337	—	—	+	74	M	9-10	3+
345	—	—	+	71	M	9-9.5	3
304	—	—	+	68	A	11	2+
314	—	—	+	62	A	10	2+
344	—	—	+	76	MF	10-11	2+
335	—	—	—	67	A	10	3+
334	—	—	—	62	MF	11	3+
309	—	—	—	66	A	10	2+
333	—	—	—	69	A	10—	2+
323	—	—	—	55	MF	10-11	2+
340	—	—	—	57	MF	11	2+
332	—	—	—	72	MF	10-11	2+
328	—	—	—	68	MF	10-10.5	2
331	—	—	—	65	A	9.5-10	2

* The prominence of slow waves was judged on a relative scale (+++, ++, + and —) for each test separately, although the absolute voltage and prominence of slow waves were much greater under the influence of insulin and hyperventilation than in the routine record. For full definition of types of electroencephalograms see Davis.¹ A indicates regular alpha pattern; M, mixed pattern, with alpha activity plus faster and slower waves; MF, mixed fast pattern, with alpha activity and faster waves; MS, mixed slow pattern, with alpha activity and slower waves, and B, low voltage (beta) pattern. The “normality rating” scale extends from 1 (most regular and normal) to 5 (abnormal dysrhythmia).

† These records are illustrated in figures 1, 2 and 3.

malty” (1, 2, 3, 4 and 5) according to the criteria described elsewhere.¹ They were also examined specifically for the presence of slow waves, either as definite episodes or as diffuse dysrhythmia. They were then judged independently (by Mrs. S. R. Blake) for the prominence of slow waves appearing after insulin and during hyperventilation. In table 2 the data are arranged in groups in order of diminishing promi-

nence of slow waves in the routine records and, within each group, according to the reaction to insulin and to hyperventilation. The general correspondence (and also the occasional divergences) in rating according to the various criteria are evident.

COMMENT

It seems clear that neither insulin nor hyperventilation induces dysrhythmia equally in all electroencephalographic records. Both the fall in blood sugar and the hyperventilation apparently accentuate pre-existing dysrhythmic tendencies and make them more evident to casual inspection. Davis and Wallace⁵ pointed out the synergistic action of a low blood sugar level and of hyperventilation in producing slow waves and the stabilizing effect of a high blood sugar level in the presence of hyperventilation. The present observations further emphasize the close relationship of the electroencephalographic reactions to low blood sugar and to hyperventilation, and also the dependence of both reactions on individual differences revealed by careful examination of the routine electroencephalogram.

The relation of the electroencephalographic changes during hyperventilation to the type of the electroencephalogram is particularly clear (table 2). None of the 3 subjects with records of the low voltage (beta) type and only 1 of the 8 subjects with tracings of the mixed fast type showed clear, slow waves, while nearly all with the mixed and mixed slow types showed them more or less prominently. The subjects with alpha patterns formed an intermediate group, of whom some did and some did not show positive reactions. My (unpublished) observations on an earlier (1939-1940) group of students showed this same stability of the beta and the mixed fast type during hyperventilation. In still another set of experiments (unpublished), carried out in collaboration with Dr. A. Graybiel, in which the rate of breathing was set for all subjects and the tidal volume measured and controlled on the basis of body weight, the results were the same.

Both the insulin test and the voluntary hyperventilation apparently serve to accentuate characteristics that are present, but less clearly evident, in the routine electroencephalogram. The alteration of the blood sugar level, although more time consuming, has the advantage that it does not require the intelligent, active cooperation of the subject and may therefore be applicable in certain cases in which the subject is uncooperative or unintelligent and the hyperventilation test is unsatisfactory or impractical.

5. Davis, H., and Wallace, W.: Factors Affecting Changes Produced in Electroencephalogram by Standardized Hyperventilation, *Arch. Neurol. & Psychiat.* 47:606 (April) 1942.

All the subjects for these tests were normal healthy college students. It would be of interest to determine the effect of the insulin-test on the electroencephalograms of abnormal subjects, particularly of known epileptic patients.

SUMMARY

Electroencephalograms were recorded on 40 healthy college students (*a*) during a routine rest period, (*b*) for forty-five minutes after intravenous injection of insulin (0.05 unit per kilogram of insulin containing 40 units per cubic centimeter), (*c*) for fifteen minutes thereafter after oral ingestion of 50 cc. of Karo corn syrup and, finally, (*d*) for three minutes of voluntary hyperventilation. The blood sugar level, the pulse rate and the blood pressure were determined systematically.

No consistent relation appeared between the electroencephalographic changes and the pulse rate or the blood pressure.

As the blood sugar level fell (to a minimum of 53 to 85 mg. per hundred cubic centimeters), the normal alpha activity of the electroencephalogram was increasingly replaced by slower waves, chiefly in the 6 to 8 cycle range. The electroencephalogram returned to normal with the restoration of the blood sugar level, but electroencephalographic changes lagged ten minutes or more behind the changes in the blood sugar.

"Slow swings," of two to five seconds' duration, often appeared in the frontal record during the height of the insulin reaction. These potential changes apparently originate in the skin of the forehead.

The appearance of conspicuous electroencephalographic changes during the insulin test correlates fairly closely with the appearance of prominent slow waves during hyperventilation and with the presence of (much less prominent) slow waves in the routine electroencephalogram. Marked electroencephalographic changes during both tests were common in the mixed and the mixed slow type of electroencephalogram, less common in the regular alpha type and rare in the low voltage and the mixed fast types.

The relative advantages of the insulin and the hyperventilation test for revealing latent electroencephalographic characteristics are considered.

RESULTS OF INSULIN AND EPINEPHRINE TOLERANCE TESTS IN SCHIZOPHRENIC PATIENTS AND IN NORMAL SUBJECTS

H. FREEMAN, M.D.

J. M. LOONEY, M.D.

R. G. HOSKINS, M.D.

AND

CORA G. DYER, M.A.

WORCESTER, MASS.

Recent investigations on carbohydrate metabolism for use in diagnosis of endocrinopathies¹ have provoked interest in their possible application to the problem of schizophrenia. Horvath and Friedman² reported that after the intravenous administration of insulin schizophrenic patients showed a delay in the hypoglycemic effect and the subsequent recovery as compared with normal subjects. Meduna, Gerty and Urse³ found an anti-insulin factor to be present in the blood of schizophrenic patients which was specific for that psychosis. Gellhorn, Feldman and Allen⁴ using the hypophysectomized-adrenomedullated rat as an assay object, obtained results somewhat contrary to those noted by these authors. The latter stated that there was no difference in the insulin content of the blood of normal and of psychotic subjects, in a quiet state. Under the stress of excitement, however, the blood insulin of psychotic (including schizophrenic) patients so increased as to have a hypoglycemic effect, a phenomenon which was never seen in excited normal subjects.

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

1. Fraser, R.; Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, *J. Clin. Endocrinol.* **4**:297, 1941.

2. Horvath, S. M., and Friedman, E.: The Effects of Large Doses of Intravenous Insulin in Psychotic Nondiabetic Patients, *J. Clin. Endocrinol.* **1**:960, 1941.

3. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: I. Anti-Insulin Effect of Blood in Cases of Schizophrenia, *Arch. Neurol. & Psychiat.* **47**:38 (Jan.) 1942.

4. Gellhorn, E.; Feldman, J., and Allen, A.: Effect of Emotional Excitement on the Insulin Content of the Blood: Contribution to Physiology of Psychoses, *Arch. Neurol. & Psychiat.* **47**:234 (Feb.) 1942.

The present study was designed to investigate the glycemic and cardiovascular effects of insulin and epinephrine with the technics suggested by Fraser, Albright and Smith.¹ It was carried out on 32 male schizophrenic patients with no evidence of physical disease and on 20 normal men.

All subjects were studied in a fasting state, reclining quietly in bed throughout the period of the test. After a preliminary venipuncture for determination of the fasting blood sugar, insulin was injected intravenously in amounts of 0.1 unit per kilogram of body weight. The blood sugar was then determined at half-hour intervals for the next two hours. Immediately subsequent to the last venipuncture, epinephrine hydrochloride (1:1,000) was injected intramuscularly in amounts of 0.01 cc. per kilogram of body weight. Samples of blood were again taken thirty and sixty minutes later. Before each venipuncture the blood pressure and the pulse rate were measured to determine the possible effects of the substances on the autonomic nervous system. The patients and half of the normal subjects lived on the routine hospital diet, which was rather high in carbohydrate. The other 10 normal subjects lived outside the hospital and may have had a somewhat different diet. All blood sugars were measured by a single person, the Folin-Wu technic (alkaline tartrate colorimetric method) being used.

The ages of the patients ranged from 15 to 46 years, the average being 30 years. They had been confined to the hospital from four days to fifteen years at the time of the test, the mean period being four years. Nineteen subjects had been hospitalized for less than one year. The diagnoses included all the recognized subtypes of schizophrenia. The normal subjects were somewhat younger than the patients, their ages ranging from 17 to 31 years, with an average of 24 years. This difference in age between the two groups, however, is of no importance from the physiologic point of view.

The mean values for the blood sugars obtained during the study are shown in table 1. The control figures were essentially the same for the two groups, the difference of 3 mg. being insignificant. A half-hour after the injection of insulin the mean for the normal subjects decreased to a level of 29.6 mg. per hundred cubic centimeters, while the corresponding value for the patients was 39.2 mg. per hundred cubic centimeters.⁵ One hour after the injection the mean values were 61.1 mg. for the normal subjects and 63.6 mg. for the patients. The difference

5. For another group of 17 schizophrenic patients whose blood sugars were measured by a different technician (Miss Anne Walsh), the mean value thirty minutes after injection of insulin was 51.3 mg. per hundred cubic centimeters, a result which corroborates to an even greater degree the differences already cited.

between the two groups had been reduced from 9.6 mg., in the previous reading, to 2.5 mg. This seems to indicate that the phase of recovery from the hypoglycemic level was more active in the normal subjects. During the next hour the values for the two groups were essentially similar. Up to this point, then, the trend indicates a greater resistance to insulin, and possibly a less rapid recovery from the hypoglycemic phase, of the patients. As the recovery from the hypoglycemia is presumably due, at least in part, to endogenous adrenomedullary activity,⁶ with subsequent mobilization of sugar into the blood stream, this observation is of interest as compared with the results obtained after epinephrine was injected. The levels of blood sugar two hours after the injection of insulin, although not quite back to the original values, were

TABLE 1.—*Means of Values for Blood Sugar, Blood Pressure and Pulse Rate of Twenty Normal and Thirty-Two Schizophrenic Subjects Obtained During the Course of Insulin and Epinephrine Tolerance Tests*

	Fasting	After Insulin				After Epinephrine	
		0.5 Hr.	1 Hr.	1.5 Hr.	2 Hr.	0.5 Hr.	1 Hr.
Blood sugar (mg. per 100 cc.)							
Normal.....	87.1	29.6	61.1	75.3	79.6	105.7	132.3
Schizophrenic patients.....	90.1	39.2	63.6	73.1	78.8	101.3	118.8
Systolic blood pressure (mm. of mercury)							
Normal.....	119.7	124.6	117.1	111.1	110.9	130.7	130.7
Schizophrenic patients.....	109.2	114.8	108.9	107.1	103.5	115.6	115.5
Diastolic blood pressure (mm. of mercury)							
Normal.....	76.6	70.0	67.2	69.9	70.6	63.8	67.6
Schizophrenic patients.....	74.0	68.6	65.5	67.4	66.9	65.8	66.2
Pulse rate (beats per minute)							
Normal.....	72.0	83.8	69.5	66.5	65.3	72.1	76.6
Schizophrenic patients.....	69.2	72.8	73.5	69.7	69.1	76.3	77.8

used as control figures for the epinephrine tolerance test. These readings were similar for the two groups; so it may be considered that they started at the same base line. A half-hour after the injection of epinephrine the mean for the normal subjects had risen 26.1 mg., and in one hour 52.7 mg. per hundred cubic centimeters. The corresponding increases in blood sugar for the patients were 22.5 and 40.0 mg. per hundred cubic centimeters. The response to exogenous epinephrine was definitely less in the patients; this seems to corroborate the previous observation of a probable lessened reactivity to endogenous adrenal activity.

The results discussed heretofore have been limited only to trends and give little indication of the individual changes. These are shown

6. Cannon, W. B.: *The Wisdom of the Body*, New York, W. W. Norton & Company, Inc., 1932, p. 113.

in figure 1. Each level of the blood sugar at a given time in the procedure is represented by a black dot (for patients) or by an open circle (for normal subjects). The fasting levels show a similar distribution for the two groups of subjects, except in the case of 2 patients whose blood sugars were 119 and 127 mg. per hundred cubic centimeters. At the half-hour point, however, there is a distinct difference. The 20 normal subjects are grouped compactly between the levels of 19 and

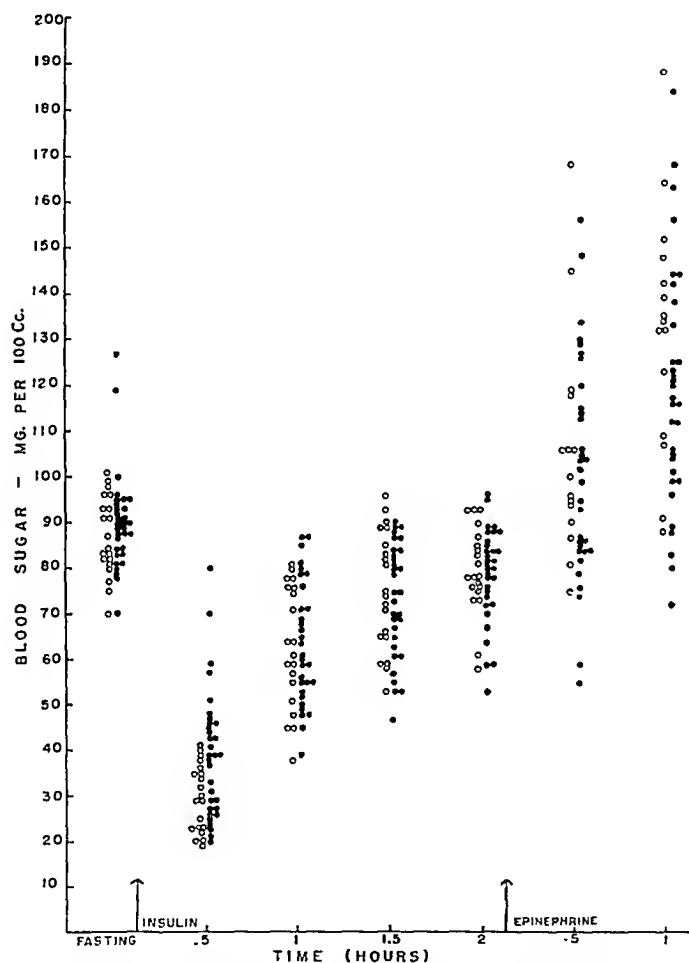


Fig. 1.—Frequency distributions of individual values for blood sugar obtained during the course of insulin and epinephrine tolerance tests on 32 male schizophrenic subjects (black dots) and 20 normal men (open circles).

41 mg. per hundred cubic centimeters. Within this range are found the values for 19 of the patients, or 59 per cent of the total number. The other 13 patients had blood sugar levels that were higher than any of the normal subjects, up to 80 mg. per hundred cubic centimeters. At the next reading, a half-hour later, the values for the normal subjects were again essentially at the same levels as those for the patients, which

indicates their seemingly more rapid recovery. During the next hour the values for the two groups continued to show a similarity of distribution. It should be noted that after the administration of insulin the range of values was slightly increased in comparison with the fasting levels, except at the thirty minute period in the case of the normal subjects. This means that in the hypoglycemic phase the normal subjects reacted to the acute effects of insulin much more homogeneously as a group than did the schizophrenic patients, but that in the stage of recovery the subjects in the two groups differed more widely from each other than during the control period.

After the administration of epinephrine the levels of blood sugar scatter widely, much more so than after the injection of insulin. This may be due to the fact that intramuscular injection affords many more possibilities for individual differentiation on account of the variation in blood supply than does the intravenous route. Another possibility may be that a downward trend of the blood sugar level is more limited, physiologically than an upward trend. The distributions for the two groups show great similarity to each other, however. It is only in the second half-hour that the normal subjects show a trend to higher levels than do the patients. This is primarily due to the fact that the blood sugar level for many of the patients remained the same, or even decreased, in the second half-hour after the injection of epinephrine. In the case of the normal subjects there were no decreases during this time. It would seem, then, that the normal subjects tended to have a more sustained effect in this regard than did the patients.

As has been seen, the response of the blood sugar to insulin can be divided into two phases: the initial decrease, which is an index to insulin sensitivity, and the secondary rise, which shows the responsiveness to hypoglycemia. Forty-one per cent of the patients showed greater resistiveness to insulin than did any of the normal subjects. The recovery phase would seem, also, to be more sluggish than normal, as indicated by values in table 1 and figure 1. The evidence in the literature on the latter point is conflicting. Horvath and Friedman² stated that schizophrenic patients are less reactive in this respect. Meduna, Gerty and Urse³ found that serum from schizophrenic patients shows an insulin-inactivating effect over a longer period than does normal serum. We have endeavored to clarify this point by determining the relationship between the blood sugar levels at the thirty minute period, that of maximum hypoglycemia, and the changes in blood sugar in the next thirty minutes, at which time there is the greatest degree of recovery. The results are seen in the scatter diagram in figure 2. There is a negative correlation between the thirty minute values and the changes in the next half-hour, which indicates that the more intense the hypoglycemia the greater the rebound from it. For example, a

blood sugar, level of 20 mg. per hundred cubic centimeters will increase 40 mg. per hundred cubic centimeters in the next thirty minutes, while the corresponding change for a blood sugar reading of 60 mg. will be only 0 to 5 mg. per hundred cubic centimeters. Thus, the change is dependent on the hypoglycemic level. Since the schizophrenic patients, whose blood sugars lay within the normal range, showed the same increase as did the nonpsychotic subjects, it may be concluded that the recovery from hypoglycemia was adequate in the patients and that their apparent sluggishness was due solely to the fact that the blood sugar level of some of the psychotic subjects was not low enough to activate the blood sugar-raising mechanisms.

The cardiovascular reactions following the administration of insulin and epinephrine are shown in table 1. The characteristic changes with

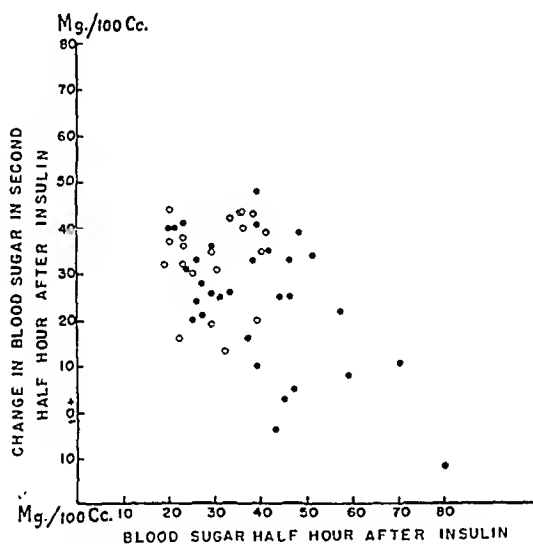


Fig. 2.—Scatter diagram illustrating the relationship between the blood sugar values obtained thirty minutes after the injection of insulin and the change from such levels in the subsequent thirty minutes, as observed in 32 male schizophrenic subjects (black dots) and 20 normal men (open circles).

insulin were an increase in systolic pressure, a decrease in diastolic pressure and an increase in pulse rate. The greatest changes were usually seen at the period of maximum hypoglycemia. Subsequently, there was a resumption to or below the control level, which may have been due to the prolonged rest in bed. Epinephrine resulted in a similar picture. There was a tendency to a greater degree of reactivity in the normal subjects. After insulin they showed an average increase in pulse rate of 12 beats per minute, as compared with 4 beats per minute for the patients. After injection of epinephrine their systolic blood pressure increased 20 mm. of mercury and their pulse rate 12 beats

per minute, as compared with a corresponding change of 12 mm. of mercury and 9 beats per minute for the psychotic group.

While this greater reactivity of the normal subjects in the blood pressure and the pulse rate parallels the greater changes in blood sugar, there is no relationship between the cardiovascular and glycemie variations within the individual subject. There may undoubtedly be a common factor, but it is not apparent on a simple basis. In addition, the reactions after insulin show no correlations with those after epinephrine in blood sugar content blood pressure or pulse rate, so that the role of the adrenomedullary secretion in the insulin reaction cannot be a dominant one.

The hypoglycemic reaction to insulin showed no relationship to age, duration of hospitalization or subtype of psychosis.

TABLE 2.—*Means of Values for Blood Sugar Obtained in the Course of Two Insulin and Epinephrine Tolerance Tests on Nine Schizophrenic Subjects, with Average Differences Between Readings Taken at Similar Times*

	Fasting	After Insulin				After Epinephrine	
		0.5 Hr.	1 Hr.	1.5 Hr.	2 Hr.	0.5 Hr.	1 Hr.
Mean values on first test..... (mg. per 100 cc.)	86.1	41.7	65.1	76.4	82.3	111.9	119.7
Mean values on second test..... (mg. per 100 cc.)	85.7	40.2	60.8	76.0	77.1	99.5	108.1
Average individual differences..... (mg. per 100 cc.)	7.8	4.8	10.4	15.9	7.7	24.6	22.9

The subjective reactions to insulin are of some interest. The characteristic symptoms during the hypoglycemic phase included a varying degree of fatigue and drowsiness, slight blurring of vision, sweating, tachycardia and hunger. No subject lapsed into unconsciousness despite the low levels of blood sugar. There was a good deal of individual variation in symptoms. When they were pronounced, the blood sugar was always low. However, in some subjects with low values after insulin few signs were evident. Thus, the relationship between the blood sugar level and these attendant phenomena was not great.

In order to evaluate the consistency of the figures obtained, insulin and epinephrine tolerance tests were repeated on 9 schizophrenic subjects with the same doses of the substances and under exactly similar conditions. These repetitions were made not later than one week after the first test in all but 1 case, in which the test was done after an interval of two months.

The average values for the two tests are shown in table 2. The means of the values for insulin tolerance were similar, particularly at the half-hour reading, which indicates, therefore, the reliability of

this figure. Two hours after the injection of insulin the figures for the second test were slightly lower than those for the first. After injection of epinephrine, however, there was a greater difference between the two readings. The values obtained in the first test were quite comparable to those for the larger group of patients. On repetition, however, the mean blood sugar levels were 11 mg. per hundred cubic centimeters lower. The reason for this lesser reaction is difficult to explain in view of the similarity of the previous portion of the curve. At any rate, the result does not invalidate the difference in values between the larger group of patients and the normal subjects, but strengthens it. Since the mean values show only the general trend, we have computed the variation between the two blood sugar values for each subject taken at identical points on the curve. For the insulin tolerance the average difference between the two readings was usually under 10 mg.⁷ per hundred cubic centimeters. At the point of maximum reaction, it was no greater than 4.8 mg. per hundred cubic centimeters. Since this is less than the difference between the large group of patients and the normal group, it would seem that these results are reliable. This appears to be particularly true since the reactions of the normal subjects were much more homogeneous and on that basis would be expected to show less variation for the individual subject. One would assume, therefore, considerable consistency in this procedure.

The case is somewhat different with epinephrine. Not only did the subjects vary widely from each other in their reaction to this substance, as shown in figure 1, but there was a good deal of fluctuation in the reaction of each subject. The average variation lay between 20 to 25 mg. per hundred cubic centimeters, a figure which may cast some doubt on the reliability of the difference between normal and schizophrenic subjects. Whether this procedure is sufficiently consistent to be reliable is at present a question.

COMMENT

The results of the study indicate that a certain proportion of schizophrenic patients show less responsivity to insulin than do normal subjects. Thus, from this point of view, the patients can be divided into two types, a differentiation which is not paralleled by variations in the psychiatric status. Our results are in agreement, therefore, with those of Meduna, Gerty and Urse.³ They are not consistent with the conclusions of Gellhorn, Feldman and Allen,⁴ who postulated a predominance of vagoinsulin influence in schizophrenic patients as compared with normal subjects, but demonstrable only in a state of excitement. Our

7. The value of 15.9 mg. per hundred cubic centimeters at the one and one-half hour point is due primarily to the variation in 1 patient of 53 mg. per hundred cubic centimeters.

results for the blood sugar, on the basis of the theory of an autonomic imbalance, suggest greater reactivity in the sympathicoadrenal sphere in the patients, since the hypoglycemic results of insulin were apparently antagonized. However, since this theory does not seem to coincide with the characteristic features of the schizophrenic state, some other explanation must be forthcoming. The specific factors responsible for the insulin sensitivity are probably of endocrine origin, since insulin resistance has been noted to be a feature of endocrinopathies involving the adrenal cortex, the thyroid and the pituitary gland.¹ It is of interest that hypometabolism⁸ and an abnormal reactivity to a glycerin extract of adrenal cortex⁹ have been characteristic of many cases of schizophrenia. The role played by the carbohydrate metabolism of the liver and tissues, independent of or associated with such hormonal factors, offers further problems.

Whatever its causation, insulin insensitivity in patients with schizophrenia is another example of the general tissue resistance to change noted by Angyal, Freeman and Hoskins.¹⁰ This observation may throw some light on the reason for the enormous doses of insulin required to produce coma in some schizophrenic patients. It also offers a lead for further investigations into the carbohydrate metabolism of the central nervous system in cases of this psychosis.

SUMMARY

An investigation was made of the glyceimic and autonomic reactions of 32 schizophrenic and 20 normal men. Forty-one per cent of the patients showed some degree of resistance to insulin. The reactions to hypoglycemia were the same in the two groups. A lessened reactivity in blood sugar following the injection of epinephrine was noted in the patients. In general, the normal subjects showed greater changes in the blood pressure and pulse rate, paralleling the differences in the blood sugar between the two groups.

Worcester State Hospital.

8. Hoskins, R. G., and Sleeper, F. H.: Organic Functions in Schizophrenia, *Arch. Neurol. & Psychiat.* **30**:123 (July) 1933.

9. Freeman, H., and Hoskins, R. G.: Comparative Sensitiveness of Schizophrenic and Normal Subjects to Glycerin Extract of Adrenal Cortex, *Endocrinology* **18**:576, 1934.

10. Angyal, A.; Freeman, H., and Hoskins, R. G.: Physiologic Aspects of Schizophrenic Withdrawal, *Arch. Neurol. & Psychiat.* **44**:621 (Sept.) 1940.

CEREBRAL DYSRHYTHMIA IN RELATION TO ECLAMPSIA

MILTON ROSENBAUM, M.D.

AND

GEORGE L. MALTBY, M.D.

CINCINNATI

The toxemias of pregnancy are usually classified as (1) preeclampsia (toxemia grade 1, or grade 2 in some clinics) and (2) eclampsia, this term being reserved for the condition in which convulsions or coma develops in the presence of the toxemia. The cause of these toxemias is not known. Most authorities believe that they are etiologically similar, and therefore a single disease entity.¹ However, why one patient has convulsions as part of the syndrome and another remains free of seizures is not clear. It is with this aspect of the problem of the toxemias that this paper will be concerned.

In recent years, with the aid of the electroencephalographic technic, a good deal of light has been shed on the problem of convulsive disorders. Many aspects of the clinical picture of the toxemic syndrome suggested the necessity of electroencephalographic studies. In a preliminary report we have briefly discussed our observations on a small series of eclamptic and preeclamptic patients.² This communication deals further with the electroencephalographic patterns and the family histories in a larger group of similar patients.

MATERIALS AND METHODS

Forty unselected patients, 20 of whom had eclampsia and 20 preeclampsia, were included in this study. With the exception of 4 patients (3 with eclampsia and 1 with preeclampsia), all had been admitted to the obstetric service of the Cincinnati General Hospital during the past five years. Each patient met the requirements recently given by Dieckman¹ for the diagnosis of eclampsia and preeclampsia. The symptoms, which included hypertension, edema, albuminuria and convulsions, are summarized in tables 1 and 2.

A thorough history was obtained on each patient by one of us emphasizing the following points: (1) history of previous convulsions, (2) history of convulsive disorders in the family (including eclampsia) and (3) history of convulsions following the toxemia.

From the Departments of Psychiatry, Neurosurgery and Neurology, University of Cincinnati College of Medicine and Cincinnati General Hospital.

1. Dieckman, W. J.: *The Toxemias of Pregnancy*, St. Louis, C. V. Mosby Company, 1941.

2. Maltby, G. L., and Rosenbaum, M.: *The Relation of Cerebral Dysrhythmia to Eclampsia: Preliminary Report*, Proc. Soc. Exper. Biol. & Med. **50**:10-12, 1942.

Electroencephalographic tracings were recorded for each patient from one week to five years after the attack of the toxemia for which they had been in the hospital. These data are recorded in table 3. It is to be noted that 75 per

TABLE 1.—*Summary of Pertinent Data Related to the Diagnosis of Eclampsia in 20 Patients*

	Age, Year	Color	No. of Pregnancies	Pregnancy in Which Attack Occurred	Blood Pressure (High)	Urinary Albumin	Edema	Serologic Reaction
1	24	B	5	1st, 4th, 5th	200/130	+++	+	—
2	23	B	3	3d	190/100	++	+	—
3	24	B	3	3d	170/120	+	+	—
4	18	B	2	2d	180/100	++	+	—
5	22	B	5	5th	170/100	+	+	+
6	20	W	1	1st	140/ 90	++	+	—
7	15	B	1	1st	196/110	++	—	—
8	25	B	6	6th	210/130	++	+	—
9	17	B	1	1st	180/110	+	+	+
10	22	W	1	1st	176/110	+++	+	—
11	24	W	1	1st	160/ 95	++	—	—
12	18	B	3	3d	190/110	+++	+	—
13	19	B	2	1st	154/102	++	+	—
14	41	B	9	9th	212/134	++++	+	—
15	36	W	2	1st	160/100	+	+	—
16	18	W	1	1st	200/110	+++	+	—
17	19	W	1	1st	175/110	+	+	—
18	32	B	12	9th	190/140	—	—	—
19	32	B	3	3d	138/106	+++	+	—
20	25	B	6	2d	210/115	++	—	—

TABLE 2.—*Summary of Pertinent Data Related to the Diagnosis of Preeclampsia in 20 Patients*

	Age, Year	Color	No. of Pregnancies	Pregnancy in Which Attack Occurred	Blood Pressure (High)	Urinary Albumin	Edema	Serologic Reaction
1	24	B	2	2d	190/110	+	—	—
2	23	B	5	5th	200/120	++	+	—
3	35	B	6	6th	225/115	++	+	—
4	32	W	2	2d	170/100	++	+	—
5	32	W	6	6th	174/110	—	—	—
6	42	B	15	14th, 15th	214/120	+	+	—
7	36	B	8	8th	150/ 90	—	+	—
8	27	W	4	4th	190/115	+	+	—
9	24	B	1	1st	164/100	++	+	—
10	38	W	6	6th	240/132	++	+	—
11	17	W	2	2d	158/115	++	—	—
12	30	B	5	5th	168/110	—	+	+
13	32	W	5	5th	154/ 90	—	+	—
14	43	W	12	12th	148/ 92	+	+	—
15	23	B	2	2d	150/102	—	—	+
16	16	B	1	1st	184/104	+	—	—
17	16	B	1	1st	160/110	+	—	—
18	31	W	2	1st	220/140	+++	+	—
19	42	W	10	10th	235/117	++	+	—
20	16	B	1	1st	160/130	+	+	—

cent of the tracings of the eclamptic groups (15 patients) were taken from six months to five years after the attack, while in the preeclamptic group (10 patients) 50 per cent of the tracings were taken from one to two years after the attack. The intervals are adequate in most, if not in all, instances to exclude postconvulsive

changes as a cause of the abnormal tracings. In this respect it is interesting that of the 10 tracings recorded for the preeclamptic patients within two weeks after delivery, only 2 revealed abnormalities. These observations were of aid in ruling out any obvious cerebral dysrhythmias which may have arisen from the pregnancy and parturition.

The electroencephalographic technic consisted of six lead monopolar recordings, with the lobe of the ear as a reference point. The leads were taken from the frontal, parietal and occipital regions. Short periods of hyperventilation were included in each record. From the scalp electrodes the potentials were led off to Grass amplifiers and recorded on a three channel ink writer. The records were analyzed according to the standards suggested by Gibbs and Gibbs,³ Jasper and Kershman⁴ and Davis,⁵ and more recently by Williams,⁶ which include criteria for frequency, amplitude, wave form and general stability. The tracings were interpreted by one of us (G. M.) without knowledge of the patient's obstetric diagnosis and history.

TABLE 3.—*Time Interval Between Delivery and Recording of the Electroencephalogram in the Eclamptic and the Preeclamptic Group*

Time After Delivery in Which Electro- encephalogram Was Recorded	Number of Patients			
	Eclampsia		Preeclampsia	
	Number	Percentage	Number	Percentage
1 wk.	2	10	6	30
2 wk.	3	15	4	20
6 mo.	1	5	0	..
1 yr.	6	30	4	20
2 yr.	5	25	6	30
3 yr.	1	5	0	..
5 yr.	2	10	0	..
Total.....	20	100	20	100

RESULTS

The results of this study are graphically depicted in figures 1 and 2. Thirteen (65 per cent) of the 20 patients with eclampsia had abnormalities (cerebral dysrhythmias) in their electroencephalograms, while only 2 (10 per cent) of the patients with preeclampsia had similar abnormalities (fig. 1). The abnormalities encountered (figs. 3 and 4) were for the most part similar to those seen with the convulsive disorders (epilepsy) in that they revealed dysrhythmias characterized by slow waves with increased voltage.

3. Gibbs, F. A.: Interpretation of the Electroencephalogram, *J. Psychol.* 4:365, 1937. Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*, Cambridge, Mass., Lew A. Cummings Co., 1941.

4. Jasper, H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, *Arch. Neurol. & Psychiat.* 45:903 (June) 1941.

5. Davis, P. A.: Technique and Evaluation of the Electroencephalogram, *J. Neurophysiol.* 4:92, 1941.

6. Williams, D.: The Significance of an Abnormal Electroencephalogram, *J. Neurol. & Psychiat.* 4:257, 1941

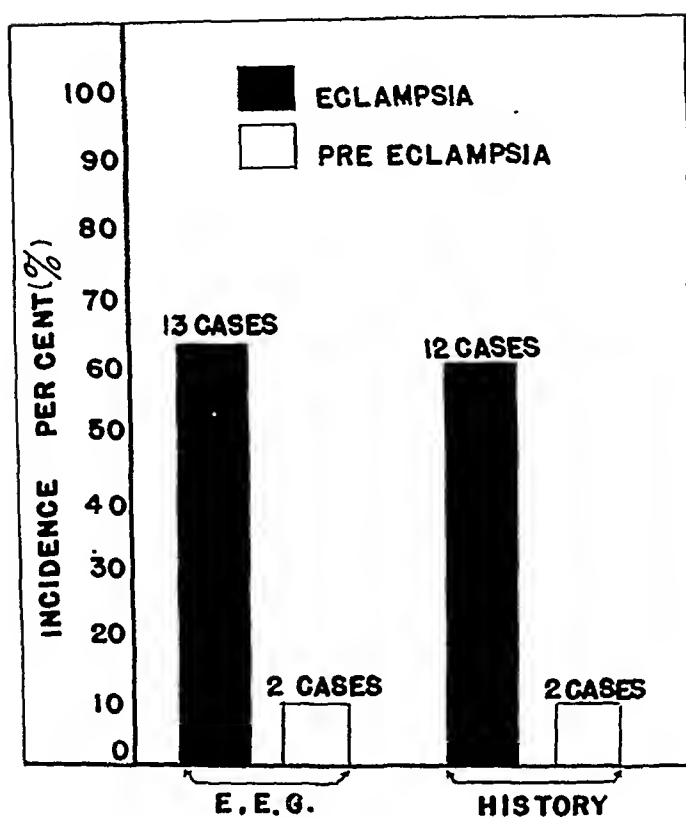


Fig. 1.—Incidence of abnormal electroencephalograms and of family histories of convulsive disorders in 20 eclamptic and 20 preeclamptic patients.

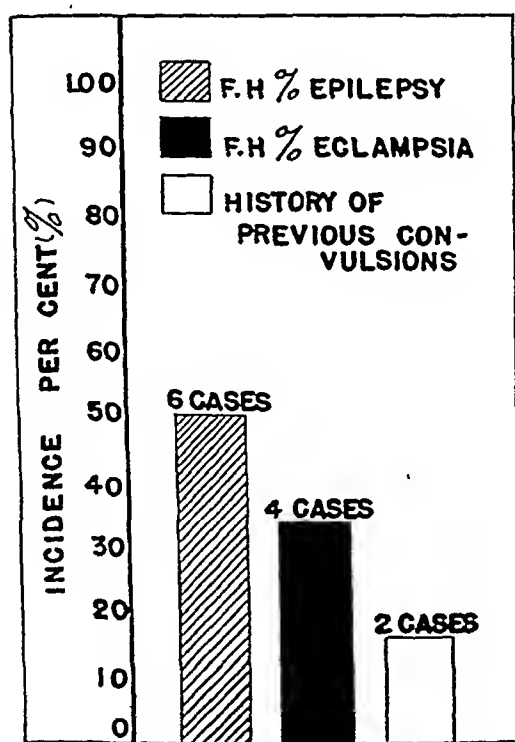


Fig. 2.—Analysis of 12 cases of eclampsia with a history of convulsive disorders. In 6 cases there was a family history of epilepsy, in 4 cases a family history of eclampsia and in 2 cases a history of previous convulsive episodes in the patient.

The historical data revealed that a convulsive diathesis existed in 12 (60 per cent) of the eclamptic patients, as contrasted with 2 (10 per cent) of the preeclamptic patients (fig. 1). The data on the eclamptic group have been analyzed in figure 2. Six of the patients gave a history of epilepsy in one or more members of the immediate family. In 4 additional patients the history of convulsions was limited to an attack of eclampsia in one member of the immediate family. In 1 of these 4 patients eclampsia developed in the first pregnancy, and since then she has had frequent grand mal attacks (epilepsy) and is responding well to dilantin therapy. The remaining 2 patients gave a history of

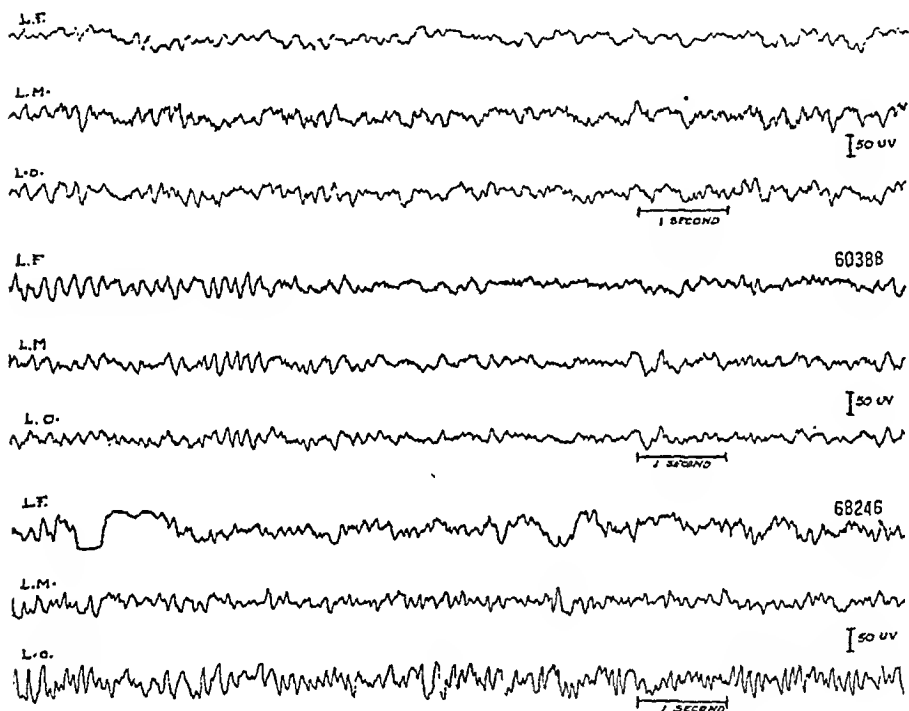


Fig. 3.—The electroencephalographic tracings for 3 eclamptic patients recorded from the left frontal, motor and occipital areas. These recordings were made during the resting stage. Note the obvious scattered slow waves, many of high voltage, and the general appearance of instability in all three records.

convulsive episodes previous to the attack of eclampsia. One of these patients had an interesting history in that as a child she suffered from petit mal episodes and in adolescence there was an occasional grand mal attack. In her first pregnancy toxemia developed, and during the eighth month she went into severe "status epilepticus." After recovery the patient had more frequent grand mal attacks, which recently have been controlled by dilantin therapy.

A few comments regarding the data in tables 1 and 2 may be of interest. Of the 20 eclamptic patients, 14 were Negroes and 6 were white

persons, while 11 of the preeclamptic patients were Negroes and 9 were white persons. These figures probably reflect the incidence of white persons and Negroes in the obstetric service. The average age of the eclamptic patients was 24 years, as compared with a corresponding age of 29 years for the preeclamptic patients. Ten (50 per cent) of

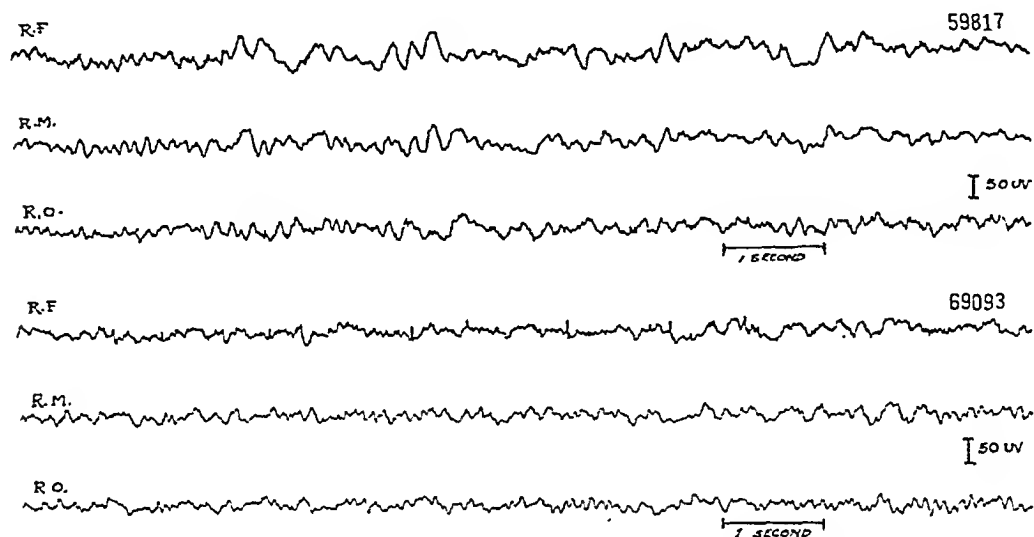


Fig. 4.—Electroencephalographic tracings for the 2 eclamptic patients with a history of previous convulsions. The recording was done during the resting stage. Note the prominent abnormalities, consisting of diffuse, high voltage, slow waves.

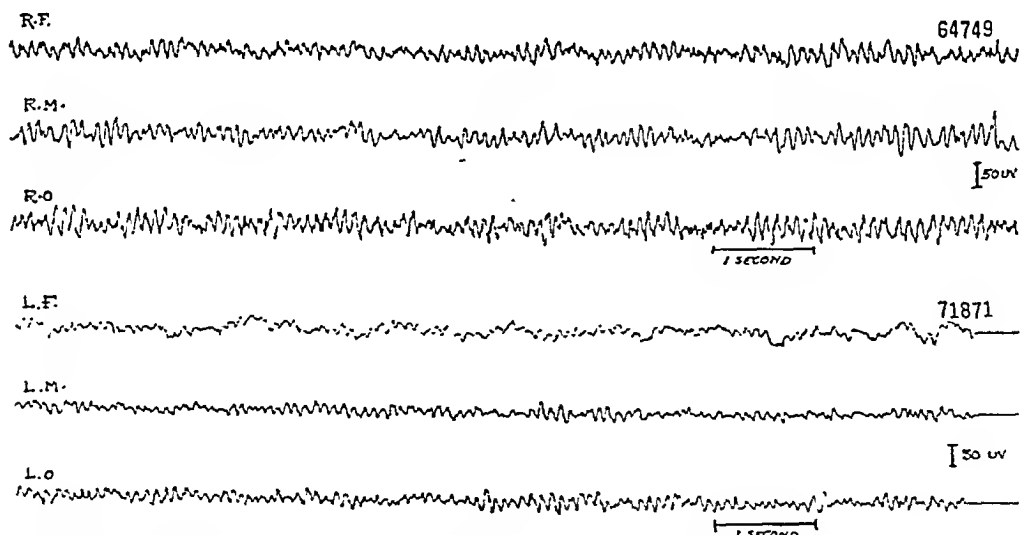


Fig. 5.—Normal electroencephalograms of 2 preeclamptic patients, showing a stable, 10 per second rhythm of normal voltage.

the eclamptic patients had the attacks in the first pregnancy, while only 5 (20 per cent) of the preeclamptic patients were stricken in the first pregnancy. Also, there were 7 primiparas with eclampsia as compared with 4 with preeclampsia. The foregoing data regarding the age incidence and the increased proportion of primiparas with eclampsia is in agreement with the observations of other authors.¹

COMMENT

In recent years it has been demonstrated that patients suffering from convulsive disorders in the form both of "idiopathic" and of "symptomatic" epilepsy have more or less characteristic types of abnormalities in their electroencephalograms. Lennox coined the term "cerebral dysrhythmia" to indicate such abnormalities.⁷ The excellent studies of Lennox, Gibbs and Gibbs⁸; Robinson⁹ and Löwenbach¹⁰ revealed that the cerebral dysrhythmia is an inherited characteristic, and it is this factor which predisposes one to the convulsive disorders. Although only 0.5 per cent of the general population suffers from clinical "epilepsy," it has been estimated in preliminary sampling by Lennox, Gibbs and Gibbs¹¹ that approximately 10 per cent of normal persons exhibit abnormalities similar to those seen in patients with seizures or related conditions. These persons with "asymptomatic dysrhythmia" may, of course, go through life without manifesting convulsive phenomena. On the other hand, in the face of conditions which affect the central nervous system, either by structural changes, such as brain tumor, trauma, encephalitis or syphilis, or by metabolic or physiopathologic changes due to drugs, toxins, changes in the chemical constituents of the blood, etc., a predisposed person is more likely to have convulsions.⁷

Rosenbaum, Lewis, Piker and Goldman¹² noted that convulsions developed in 9 per cent of a large series of patients with delirium tremens, and they concluded that one of the basic etiologic factors responsible for the convulsion was the underlying predisposition in the form of an inherent cerebral dysrhythmia. Recently Foster¹³ studied the association between convulsive seizures and rheumatic heart disease. He noted that the familial incidence of convulsive seizures or migraine appears in cases of rheumatic heart disease associated with seizures six times as frequently as in cases of rheumatic heart disease without seizures.

7. Lennox, W. G.: *Science and Seizures*, New York, Harper & Brothers, 1941.

8. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. W.: *Inheritance of Cerebral Dysrhythmia and Epilepsy*, *Arch. Neurol. & Psychiat.* **44**:1155 (Dec.) 1940.

9. Robinson, L. J.: *Cerebral Dysrhythmias in Relatives of Epileptic Persons*, *Arch. Neurol. & Psychiat.* **44**:1109 (Nov.) 1940.

10. Löwenbach, H.: *The Electroencephalogram in Healthy Relatives of Epileptics*, *Bull. Johns Hopkins Hosp.* **65**:125, 1939.

11. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: *The Inheritance of Epilepsy as Revealed by the Electroencephalogram*, *J. A. M. A.* **113**:1002 (Sept. 9) 1939.

12. Rosenbaum, M.; Lewis, M.; Piker, P., and Goldman, D.: *Convulsive Seizures in Delirium Tremens*, *Arch. Neurol. & Psychiat.* **45**:486 (March) 1941.

13. Foster, D. B.: *Association Between Convulsive Seizures and Rheumatic Heart Disease*, *Arch. Neurol. & Psychiat.* **47**:254 (Feb.) 1942.

The high incidence (65 per cent) of cerebral dysrhythmias, together with the high incidence (60 per cent) of a positive family history of convulsive disorders, found in this group of 20 eclamptic patients is striking. These results strongly suggest that there may be a primary cerebral dysrhythmia present in patients with the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear. These factors may help to explain the well known fact that eclampsia is more common in young primiparas. Signs of cerebral involvement have been noted pathologically, and of course clinically. Minute hemorrhages are frequent; edema and congestion are common, and occasionally gross cerebral hemorrhages have been observed in patients dying of toxemia. The convulsions have been considered to be dependent on the cerebral anoxemia resulting from cerebral vasoconstriction and/or edema.¹ These histopathologic and physiopathologic changes would thus constitute the cerebral "insult," or "trigger mechanism."

There is a paucity of material in the literature concerning the family history of convulsive disorders in cases of eclampsia. Apparently, most authors have limited the historical data to the question of a family history of eclampsia alone. Various citations have been made regarding isolated cases in which there was a family history of eclampsia. In the present study 4 of the eclamptic patients had such a history. However, the more detailed historical data gathered for this series point to a rather high incidence of convulsions (60 per cent) in the eclamptic group and further emphasize the important role of a "constitutional" predisposition to convulsions in patients with eclampsia.

Patients with epilepsy do not as a rule have more seizures during pregnancy.¹⁴ However, if toxemia develops in a patient with epilepsy, it may be a different story. The case cited previously is pertinent. In childhood there had been petit mal attacks, and an occasional grand mal attack had occurred during adolescence. In the eighth month of the patient's first pregnancy toxemia and "status epilepticus" developed. Patients have had "idiopathic epilepsy" after an attack of eclampsia, and this course was experienced by 1 of the eclamptic patients considered previously in this study. Dexter and Weiss¹⁵ reported the case of a patient with a negative personal history for epilepsy in whom grand mal seizures developed after eclampsia. A similar case was noted by DeLee.¹⁶ It might be argued that such patients should not

14. Lennox, W. G., cited by Dexter and Weiss.¹⁵

15. Dexter, L., and Weiss, S.: *Pre-Eclamptic and Eclamptic Toxemia of Pregnancy*, Boston, Little, Brown & Company, 1941.

16. DeLee, J. B.: *The Principles and Practice of Obstetrics*, ed. 7, Philadelphia, W. B. Saunders Company, 1938.

be considered as having true eclampsia, but rather as having "epileptic convulsions associated with toxemia." In our opinion the underlying factor partially responsible for the convulsion—the inherent cerebral dysrhythmia—is the same in both instances, and whether or not the patient had had clinical convulsions previous to the toxemia is of little importance.

Dieckman¹ has presented statistical data on the incidence of the various types of toxemia in 1,100 toxemic patients. If consideration is limited only to those toxemias peculiar to pregnancy (preeclampsia and eclampsia), it may be noted that 47 per cent of the patients had preeclampsia and 4.4 per cent eclampsia. Thus, 10 per cent of the patients with true toxemia of pregnancy had convulsions (eclampsia). These figures are suggestive in view of the data presented by Lennox, Gibbs and Gibbs¹¹ to the effect that about 10 per cent of the normal population is predisposed to convulsive disorders.

This study strongly suggests that a person who is predisposed to convulsions, as evidenced by an inherent cerebral dysrhythmia or a family or personal history of convulsive disorders, is likely to exhibit convulsions in the presence of toxemia of pregnancy. In the past this syndrome has been termed eclampsia.¹⁷ These studies are not concerned in any regard with the cause of the toxemia. In accord with this concept is the fact that many of the methods that have been successful in the therapy of eclampsia have depended on the use of anti-convulsant drugs (magnesium sulfate, sedatives, etc.).

It may be inferred that a careful history, together with an electroencephalogram, may be of great importance in determining in whom eclampsia may develop. Furthermore, it is apparent that the proper prophylactic therapy of such persons might include measures generally employed in the treatment of cerebral dysrhythmias (anticonvulsant drugs).

SUMMARY AND CONCLUSIONS

Thirteen, or 65 per cent, of 20 patients with eclampsia had electroencephalograms indicative of cerebral dysrhythmia, as compared with 2, or 10 per cent, of 20 patients with preeclampsia.

17. Since the term "eclampsia" refers to the toxemia of pregnancy associated with convulsions, it would seem that "preeclampsia" should refer to the same condition before convulsions appear. Thus, "preeclampsia" implies that convulsive phenomena are possible. However, our conclusions would make the term "preeclampsia" illogical. The absence of convulsions in "nonconvulsive toxemia of pregnancy" is due not to the fact that for some reason the possible convulsion has not appeared, but to the patient's innately stable cerebral rhythm. Therefore, some term other than "preeclampsia" should be used to designate "nonconvulsive toxemia of pregnancy."

Twelve, or 60 per cent, of patients with eclampsia had a family and personal history of convulsive disorders, while only 2, or 10 per cent, of the preeclamptic patients had a similar history.

It is suggested that a primary cerebral dysrhythmia may be present in those patients having the syndrome of eclampsia, and that the associated toxemia may be the "trigger mechanism" that exaggerates the inherent dysrhythmia to the degree that convulsions appear.

A careful history, together with an electroencephalogram, might be of aid in predicting in whom eclampsia may develop.

The prophylactic therapy of eclampsia may include the use of anti-convulsant drugs.

Dr. Richard Bryant and the other members of the obstetric staff cooperated in this study.

Technical assistance was given by Mrs. Edward V. Brookfield.

INTRACRANIAL EPIDERMIDS OCCURRING SIMULTANEOUSLY BELOW AND ABOVE THE TENTORIUM

HOWARD A. BLACK, M.D.

BROOKLYN

The term epidermoid (cholesteatoma) refers to a slow growing, cystic neoplasm which may occur in or beneath the scalp, within or about the orbit, in the neck, jaws, middle ear, mastoid, cranial bones or elsewhere along the craniospinal axis. The manner of origin is said to be by inclusion of epiblastic tissue during the closure of clefts or at a point of contact of ectodermal invagination with other tissues in the development of the embryo.¹ Another presumptive source is epidermal implantation resulting from trauma, an example of which has been recorded by Graumann.² Up to the time of writing 205 cases of intracranial epidermoid tumor have been recorded in the literature. Of this number there were 7 in which the lesion was situated in both the supratentorial and the infratentorial position. The purpose of this paper is to review these 7 cases and to add the eighth. The following are brief abstracts of the cases given chronologically as they appeared in the literature.

PREVIOUS CASES

CASE 1 (reported by Price,³ 1887).—L. F., a widow aged 39, was attended in the outpatient department of the Berkshire Hospital during December 1886 and January 1887. The initial symptoms were not given, but the illness was of five years' duration and was characterized as steadily progressive. One year after onset vision was lost in the right eye. Later there were attacks consisting of a sudden, queer feeling in the head, falling, dropping of articles from the hand and urinary incontinence. Examination disclosed that the right optic nerve head was white, the left one pale and the vessels of the fundi thin. Gradually the patient lost ground, suffered from recurrent convulsive seizures and died on Jan. 28, 1887.

Autopsy revealed a tumor of the brain and several areas of caseous tuberculosis in the apex of the left lung. Before the Pathological Society of London on March 3, 1887 Price presented the brain, over the base of which a large,

From the Neurological Unit of The Brooklyn Hospital.

1. Ewing, J.: *Neoplastic Diseases: A Treatise on Tumors*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 1051.

2. Graumann, G.: Ueber ein traumatisch entstandenes Cholesteatom der hinteren Schadelgrube, *Zentralbl. f. Chir.* 64:1154-1161 (May 15) 1937.

3. Price, J. A. P.: Cholesteatoma at the Base of the Brain, *Tr. Path. Soc. London* 38:24-26, 1887.

irregularly nodular, brittle tumor spread from the medulla oblongata to the optic chiasm, displacing the temporal lobes laterally. On the medulla was a smaller tumor of the same characteristics, which contained sebaceous-like material. The growth appeared encapsulated by a thin membrane which was continuous with the pia-arachnoid and had a mother-of-pearl sheen. Aside from the areas of compression the brain appeared normal. On microscopic examination numerous cholesterol crystals and the outlines of several cells devoid of nuclei were seen.

CASE 2 (reported by Frank,⁴ 1889).—A man aged 43 was admitted to an asylum for the insane at the age of 39 (1879) because of peculiar and incessant talking. On examination he was found to have left hemiparesis, prominent eyes and strabismus on the right. In May 1881 a convulsion took place, and in February 1883, paresis of the extremities of the right side developed after another convulsion. A few months later the right upper extremity alone was involved in violent, jerking movements, after which the paresis of the extremities of the right side increased. More seizures ensued, implicating sometimes the right and at other times the left side. Death occurred during a particularly severe convulsion in January 1884.

Postmortem examination revealed a transparent, glossy growth the size of a chicken's egg in the region of the right operculum, which destroyed this structure and extended in the form of numerous pea-sized masses to envelop the optic chiasm and the right optic tract. A more spongelike and transparent portion of the tumor was directed posteriorly, where it covered the cerebral peduncles and the pons. At the pontobulbar junction was another neoplasm (apparently not connected with the first) measuring 3 by 2.5 by 1 cm. Histologically the two masses were alike, showing webbing of epithelial cells and cholesterol crystals.

CASE 3 (reported by Nehr Korn,⁵ 1897).—A man aged 44 was admitted to the hospital on June 15, 1894. About 1894 he had become depressed and complained of loss of appetite and sleeplessness. During the weeks just before admission he had been restless and mentally disturbed. Examination revealed that the left pupil was larger than the right and the facial muscles were flaccid, particularly on the left side. A fissure at the left corner of the mouth and excoriations of the scalp were ascribed to syphilis. The psychologic aberrations became rapidly greater, necessitating forced feeding, and after a period of coma the patient died July 28, 1894, supposedly of dementia paralytica.

Autopsy revealed complete absence of the left frontalis and masseter muscles. In the left cerebellopontile angle was a white, crumbly mass consisting of mother-of-pearl, glossy particles of skin, in which were embedded the sixth through the tenth cranial nerves of this side. The pons and medulla were compressed and displaced to the right by the tumor. Situated in the left temporo-occipital region of the cerebrum was another and larger tumor about the size of an apple, almost covered by cerebral tissue and partly encapsulated. The temporal horn of the left lateral ventricle was partly occupied by the neoplasm, although the ependyma remained intact. A white membrane of arachnoid webbing covered the base of the growth. Microscopic examination showed keratinized, desquamated epithelium but no hair or sudorific glands. (No description of the capsule was given.)

4. Frank, C.: Ueber einen in der Dürer'schen Irrenanstalt beobachteten Fall von Cholesteatom, *Allg. Ztschr. f. Psychiat.* 46:30-38, 1889.

5. Nehr Korn, A.: Ein Fall von meningealer Perlgeschwulst, *Beitr. z. path. Anat. u. z. allg. Path.* 21:73-103, 1897.

CASE 4 (reported by Strauss,⁶ 1913).—A woman aged 32 was admitted to Mount Sinai Hospital on Oct. 5, 1909, complaining of pains in the joints, difficulty in chewing and swallowing and earache. She was the mother of three children, the youngest being 16 months old. The onset of her illness began in 1906 with disturbance of menstruation, the periods occurring every two to three months. At about this time there was an increase in weight, and headache developed. Eleven months prior to admission signs of mental derangement became evident. The headaches became more frequent and severe and were associated with nonprojectile vomiting. There was almost continuous gnashing of the teeth; the eyesight failed, and there was loss of memory for recent events, increased gain in weight, abnormal thirst and absence of menstrual flow during the last four months. Examination disclosed mental blunting. The facies were suggestive of acromegaly; the axillary and the pubic hair was sparse, and the subcutaneous fat was unusually sensitive. The optic fundi were normal. Glycosuria was present. On April 10, 1910 the patient was transferred to Montefiore Hospital. At this time the right optic nerve head was white and the left pale, and there was apparent bitemporal hemianopia. Stupor developed and terminated in death on Dec. 21, 1911.

Postmortem examination was confined to the head. On the under side of the brain a cystic, gelatinous mass extended from the inferior level of the olivary bodies to the optic chiasm. The pons was partially compressed by the largest prominence of the mass, while the region of the left basal ganglia was occupied by another large portion of the tumor, a projection of which extended into the cavity of the left lateral ventricle and another into the left frontal lobe. The neoplasm measured 4 cm. transversely and 5 cm. anteroposteriorly. The pathologic diagnosis was "cholesteatoma."

CASE 5 (reported by Bailey,⁷ 1924).—B. A., a man aged 40, was admitted to the Peter Bent Brigham Hospital on Nov. 14, 1922, complaining of loss of eyesight. In 1917 headaches prompted the patient to consult an oculist, who found that the visual acuity of the left eye was much reduced. By 1919 visual impairment had progressed to the point where he was no longer able to fulfil his duties as a salesman. During the year prior to admission there was physical weakness with loss of libido. Examination disclosed bilateral "primary" optic nerve atrophy, and vision in the right eye was restricted to perception of large objects in the lower left field. No other abnormal neurologic signs were demonstrable. On Nov. 27, 1922 a left transfrontal craniotomy was performed by Dr. Harvey Cushing. Between the optic nerves the rounded, glistening membrane of a pearly tumor, about 1 cm. in diameter, was visualized. After this portion was scooped out with a pituitary spoon, a mass the size of a golf ball was observed in the left middle fossa. This, in turn, was scooped out. It was then seen that the growth extended beyond the tentorium, and the operator followed this prolongation at least 5 cm. beyond the incisura. The cavity created by the removal of the tumor was filled with saline solution and the wound closed, no bleeding having been encountered. After a stormy course characterized by fever, fulness of the operative area and signs of meningeal inflammation, the patient improved, and he was discharged on Jan. 8, 1923. When interviewed in March 1923, he was in excel-

6. Strauss, I.: A Case of Cholesteatoma of the Brain, *J. Nerv. & Ment. Dis.* 40:257-259, 1913.

7. Bailey, P.: Further Observations on Pearly Tumors, *Arch. Surg.* 8:524-534 (Jan.) 1924.

lent physical condition but manifested mild psychologic disturbances. Pathologic examination of the material removed at operation disclosed a structure compatible with a diagnosis of epidermoid.

CASE 6 (reported by Cushing,⁸ 1932).—A neurasthenic woman aged 43 was observed in the medical wards of the Peter Bent Brigham Hospital in 1926 for mitral stenosis, aortic insufficiency and severe headache. Partial deafness and other signs pointing to a neoplasm of the left cerebellopontile angle were noted at that time. In 1924 transient double vision had occurred, and the following year gradually increasing numbness of the left side of the face and attacks of dizziness and staggering were added to the symptoms. Later, pains in the distribution of the second and third divisions of the left trigeminal nerve were the presenting complaints and led to a second admission to the hospital on May 26, 1927—this time to the surgical service. The left eye protruded and deviated inward. The left side of the face was numb, but the deafness that had been noted during the previous admission had largely disappeared. "Fairly definite right-sided pyramidal symptoms were present." She was nervous and difficult to manage, and at her own request she was discharged without operation. During 1928 the symptoms grew worse, and periods of unconsciousness began to follow the headaches. On Dec. 6, 1928 the patient was admitted to the hospital for the third time, when, in addition to the previously described clinical picture, she presented neurokeratitis of the left eye. Because it was the impression that the trouble was a meningioma of the left gasserian ganglion sheath a craniotomy was undertaken. When the region of Meckel's cavity was exposed, the remnants of the ganglion were seen stretched over the glistening surface of a cholesteatoma, about 2 cm. in diameter. The tumor was thoroughly cleaned out and supposedly entirely removed, together with its enveloping membrane. Recovery was uneventful, and the patient was discharged on Jan. 23, 1929. The immediate result of the operation was alleviation of the pain formerly present in the distribution of the trigeminal nerve, but suspicion of an infratentorial extension of the original tumor was aroused when the "cerebellar" symptoms became more pronounced (the gait was ataxic; nystagmus was present, and there was symptomatic implication of all the cranial nerves on the left side, from the sixth through the twelfth). The patient was admitted to the hospital a fourth time, and on Nov. 8, 1929 operation disclosed a large cholesteatoma in the left cerebellopontile angle. The mass, together with its capsule, was removed, but in pursuing the membrane through the incisura tentorii the operator had to leave a fragment lying against the left cerebral peduncle. Recovery was prompt, but tinnitus became a presenting complaint, from which the patient subsequently had some relief by the use of drugs.

CASE 7 (reported by Alpers,⁹ 1939).—K. M., a female, entered the hospital on March 30, 1936. Three years previously "Bell's palsy" had developed on the left side and persisted. This was followed two years later by staggering, which progressively increased, and three months before admission double vision developed. There had been no headache or vomiting. Examination gave evidence of impairment of the functions of the third and the fifth through the tenth cranial

8. Cushing, H.: *Intracranial Tumors: Notes upon a Series of Two Thousand Verified Cases with Surgical Mortality Percentages Pertaining Thereto*, Springfield, Ill., Charles C Thomas, Publisher, 1932, pp. 99-102.

9. Alpers, B. J.: *Cerebral Epidermoids (Cholesteatomas)*, *Am. J. Surg.* **43**: 55-65 (Jan.) 1939.

nerves on the left side, weakness of the right hand and "hyperactive reflexes." Operation on April 2 exposed a large tumor which extended from the upper end of the spinal cord along the brain stem on the left through the incisura tentorii and disappeared beneath the temporal lobe. All of the mass within the posterior fossa and part of that in the middle fossa was removed. Convalescence was uneventful. Microscopic examination identified the growth as an epidermoid. There was no capsule, but the presence of many polyhedral cells together with the typical gross appearance of a pearly tumor led to the diagnosis of "cholesteatoma."

There are also reports in the literature which describe minor encroachments on the supratentorial or the infratentorial compartment, as the case may be, by a tumor situated predominantly on the other side of the tentorium, as in the case recorded by Rosenstein.¹⁰ Here a huge epidermoid of the anterior and middle fossa sent sliver-like projections along either side of the pons for a short distance. However, such occurrences are not comparable to the cited cases and hence are not included in this group.

From the foregoing reports it is apparent that in 6 out of 7 instances there was nothing in either the history or the physical findings to excite suspicion concerning the true extent of the lesion. Although in the case reported by Cushing one might be led in retrospect to predict the existence of a mass situated in both the supratentorial and the infratentorial region, the difficulties encountered in arriving at the proper approach to the lesion by one so experienced in such matters indicates the pitfalls that may await others.

The following case seems to merit recording in detail since this experience indicates the difficulties encountered in establishing a diagnosis regarding the extent of the lesion even though ventriculographic studies were utilized.

REPORT OF A CASE

S. R., a 55 year old woman, was admitted to the neurologic unit of the Brooklyn Hospital under the care of Dr. Jefferson Browder on March 7, 1938. The patient complained of diminution of vision, impaired hearing in the right ear, tremors, clumsiness of the right hand and staggering gait.

The onset of the present illness was in 1930 (eight years prior to admission), when, without premonitory symptoms, a generalized convulsive seizure occurred during sleep. It was estimated that approximately fifty such attacks had taken place subsequently. At the outset the seizures came every second or third night; later, less frequently. No aura of any type had been experienced, and no resultant transitory paralysis had been observed by the family. For the next six years she was capable of carrying on her household duties and had no particular complaints except for the transient feeling of exhaustion for a day or so after each convulsive seizure. In the early part of 1937 vision was noted to be impaired—glasses had been worn for several years—consequently the eyes were reexamined

10. Rosenstein, A.: Pial Epidermoid of the Chiasmal Region, *J. Mt. Sinai Hosp.* 3:216-223 (Jan.-Feb.) 1936.

and new lenses prescribed. This failed to correct the visual disturbance. In August 1937 the family of the patient noticed an unsteadiness in her gait without tendency to fall in any particular direction. This difficulty in walking grew slowly worse. In October 1937 there was a decrease in the acuteness of hearing in the right ear. About this time clumsiness of both hands developed, more pronounced on the right than on the left. Inability to perform skilled acts with the right hand resulted in a change from "right handedness" to "left handedness." At no time had there been any headache, vomiting or double vision. This history was obtained from the husband and the sister. The patient's statements were unreliable because of an obvious memory defect.

The patient was well developed and moderately obese; she was alert, responsive and not acutely ill. The optic fundi appeared normal save for absence of the physiologic cup of the right nerve head. The plotted visual fields showed an incomplete homonymous defect of the upper left fields. A Horner syndrome was present on the left, and lateral gaze of the left eye was limited. There was no weakness of the extremities, but gross ataxia of all extremities was evident, especially of the right lower limb. The deep reflexes were very active, more so on the right than on the left; the abdominal reflexes were not elicited. The response to plantar stimulation was normal on the left side and equivocal on the right. No abnormality of somatic sensibilities was demonstrated. In walking there was swaying to either side, and the right lower extremity was swung with a circumduction movement. In turning quickly to the right there was swaying. Romberg's sign was demonstrable, and even with the eyes open the position could not be maintained. On March 9, 1938 ventriculographic examination was performed. Fifty-five cubic centimeters of fluid was removed and replaced with air. The roentgenograms taken immediately after the injection of air presented a filling defect in the posterior part of the right lateral ventricle—indication of a mass situated lateral to the region of the right thalamus. No air was visualized in the aqueduct of Sylvius or the fourth ventricle. At operation, performed by Dr. Browder, the right lateral ventricle was opened near the atrium, and on the inferior surface of the ventricle was observed a smooth, whitish membrane covering a domelike projection into the cavity of the ventricle. The mass displaced the temporal portion of the choroid plexus, as well as the glomus, anteromedially. It appeared that the ependyma was absent from over the dome of the mass, although the termination of the contiguous ependyma could not be identified grossly. The membrane was sufficiently transparent for visualization of a whitish, fragmented material beneath it. After the presenting portion of the membrane was excised, the contents of the oval cavity, measuring approximately 6 by 4 by 3 cm., were removed. This material was crumbly and about the consistency of cottage cheese. The interior of the hollow was smooth and somewhat glistening; the surrounding structures did not tend to obliterate it immediately. No diverticulum or other alteration in the continuity of the interior of the sac was present. It was thought inadvisable to attempt complete removal of the capsule. Recovery from the operation was rapid. On the fifth day after operation it was observed by gross test that left homonymous hemianopia was present. Perimetric examination performed twenty-one days after operation showed slight narrowing of the left homonymous fields. The gait improved, but the visual deficit remained about the same. The patient was discharged from the hospital on March 30, 1938. Microscopic examination of the tissue removed at operation showed the membrane was a cyst wall lined by squamous epithelium; the white, cheesy material was composed of desquamated, keratinized epithelium and cholesterol crystals. During the ensuing year several generalized convulsions occurred. For six months there was improvement in

walking; however, from January to June 1939 increasing impairment of gait was observed.

The patient was readmitted to the hospital on June 20, 1939, complaining of increasing impairment of vision and difficulty in walking. Vision had become so poor that faces could not be recognized a short distance away. Memory defects, especially for recent events, had been noted by both the patient and her relatives and had become so pronounced that at times a sentence was left incomplete, the remainder of the thought lost. The unsteadiness of gait was more pronounced than prior to operation, in 1938, and was described as loss of "sense of balance." There had been four generalized convulsions, all occurring during sleep and observed by the relatives only after they were in progress. The left hand was used for skilled acts, owing to clumsiness of the right hand. There had been no nausea, vomiting, double vision or headache. On examination the patient was alert, rational, oriented and aware of her mental blunting. Conversation was well sustained, but memory was poor in all respects, and simple arithmetical calculations were performed incorrectly. There was obvious euphoria. The site of the previous right parietal bone flap was well healed; the area of decompression was soft, flat and pulsating. There was a Horner syndrome on the left side. Both pupils reacted sluggishly to light; the optic nerve heads were pale, and the retinal veins of the left eye were somewhat full. There were pronounced dyspraxia and ataxia of the extremities bilaterally. By mensuration the right grip was slightly weaker than the left. There was no notable alteration in deep reflexes. Of the abdominal reflexes, only that of the left lower quadrant could be obtained. The response to plantar stimulation was equivocal bilaterally. Standing without support was impossible. On June 23, 1939 ventriculographic examination was performed. Seventy cubic centimeters of fluid was removed and replaced with air. Roentgenograms disclosed symmetric dilatation of the lateral and third ventricles and an air-filled space on the right side corresponding to the site of the cyst evacuated at the previous operation. Neither the aqueduct of Sylvius nor the fourth ventricle was visualized. On June 28, 1939 suboccipital exploration was carried out by Dr. Browder. The cerebellar hemispheres were unduly prominent, the right being slightly more so than the left. The cerebellopontile angles were easily visualized, and nothing abnormal was disclosed. An incision was made in the mesial aspect of the right cerebellar hemisphere. At a depth of approximately 1 cm. a thin membrane was encountered, and when this was opened, it was obvious that the lesion here was similar to that previously encountered in the supratentorial region. After removal of the contents of the mass ample room was afforded the operator for careful inspection of the cyst wall. The cavity extended rostrally to a point estimated to be at the level of the incisura tentorii, and no diverticulum or other change in the wall suggested a site of possible supratentorial connection. The mesial wall of the cyst lay directly adjacent to the thinned-out dorsolateral wall of the fourth ventricle, but at no point was there gross defect in the ependymal lining. A portion of the wall of the fourth ventricle and of the adjacent capsule of the tumor was removed in order to establish direct communication of the cavity with the fourth ventricle. The wound was closed with layer silk. Recovery from the operation was prompt and without complication. By the time of discharge, July 19, 1939, vision had improved somewhat, and the Horner syndrome had cleared. There were moderate dyspraxia and ataxia of all extremities, more pronounced on the left than on the right, and walking was accomplished with but slight assistance. Position sense was moderately defective in all extremities. Microscopic examination of the specimen removed at the second operation disclosed material similar to that observed at the first operation.

At the last observation (July 1941) the patient was able to get about without assistance in her house, although she still required slight help when walking in the street; the intellect was improved, and the euphoric state was no longer evident. The optic nerve heads showed a mild degree of pallor. Although some decomposition of purposeful movements persisted, the dyspraxia had improved considerably, particularly in the right upper extremity, which now is being used for eating and knitting. No gross sensory changes were demonstrable. Recovery has not been as complete as had been anticipated. However, the patient is capable of carrying on her household duties.

COMMENT

The first report of a case of intracranial epidermoid is cited as being published by Dumeril¹¹ in 1807. Excellent historical surveys with recapitulations of the various terms which have been applied to these tumors are to be found in articles by Critchley and Ferguson,¹² Mahoney¹³ and King.¹⁴ In 1936 Mahoney¹³ reviewed the literature and collected 142 cases of epidermoid, including the intracranial, diploic and spinal varieties. According to his figures the distribution of the neoplasm in these three situations, in the order named, is 16:3:1. In reports of large series of verified tumors of the brain¹⁵ the incidence of epidermoids has varied from 0.2 to 0.6 per cent.

The outer membrane of an epidermoid often presents a distinctive mother-of-pearl appearance, a fact that led Cruveilhier¹⁶ in 1829 to describe it under the term *tumeur perlée*. The structure is simple: An epithelial layer lying on a connective tissue base, which often attaches to pia mater,¹⁷ lines the interior of the cyst, the contents of which are formed by desquamated, keratinized epithelium. Histologically the sac membrane, often 1 or 2 mm. in thickness, is composed of stratified squamous epithelium. There is often an abundance of cholesterol crystals in the contents of the tumor, although this is not always so. The nature of the growth suggested to Sir James Paget¹⁸ the term "cutaneous

11. Dumeril, P.: Bull. Soc. Fac. de Med. **1**:32 (Feb. 19) 1807.

12. Critchley, M., and Ferguson, F. R.: Cerebrospinal Epidermoids (Cholesteatomata), Brain **51**:334-384 (Oct.) 1928.

13. Mahoney, W.: Die Epidermoide des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **155**:416-471, 1936.

14. King, J. E. J.: Extradural Diploic and Intradural Epidermoid Tumors (Cholesteatoma), Ann. Surg. **109**:649-688 (May) 1939.

15. Tooth, H.: Treatment of Tumors of the Brain and Indications for Operations, Proc. Internat. Cong. Med., London, 1913, sect. 11. Horrax, G.: A Consideration of the Dermal Versus the Epidermal Cholesteatomas Having Their Attachment in the Cerebral Envelopes, Arch. Neurol. & Psychiat. **8**:265-285 (Sept.) 1922. Mahoney.¹³

16. Cruveilhier, J.: Anatomie pathologique du corps humaine, Paris, J. B. Baillière, 1829, vol. 2, pt. I, plate 6.

17. Boström, E.: Ueber die pialen Epidermoide, Dermoide und Lipome und duralen Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1-98 (Jan.) 1897.

18. Paget, J.: Lectures on Surgical Pathology Delivered at the Royal College of Surgeons of England, London, Longmans, Green & Co., 1854, vol. 2.

proliferating cyst," although he did not restrict the designation to the epidermoid, applying it to the broader group of dermoids as well. It seems that the adoption of this term would be at once accurate, descriptive and final and would avoid the confusion that has attended the terminology of this tumor in the literature, and about which there is no definite agreement as yet.

Since the presence of an epidermoid situated intracranially is betrayed only by its pressure effects, or by altered flow of cerebrospinal fluid due to blocking of its route, one would not expect the true nature of the lesion to be suspected preoperatively. When such a tumor is exposed, the question should occur to the operator whether or not the mass visualized represents the entire extent of the tumor, since it has been shown that of 206 epidermoids located within the cranial cavity, 8 were situated in both the supratentorial and the infratentorial position. In the case just reported the original impression was that the tumor was in the posterior fossa, but plotting of the visual fields, together with the presence of dyspraxia and the history of convulsive seizures of long standing, displaced consideration of such a localization. The ventriculographic evidence was deemed consistent with the general picture presented by the patient. It was not, therefore, until the patient took a turn for the worse, after having made a start toward recovery after the first operation, and exhibited an accession of the so-called cerebellar signs that consideration was given to the possibility of a similar lesion's being situated in the posterior cranial fossa. Had the injected air entered the aqueduct of Sylvius it is probable that the presence of two tumors would have been demonstrated initially by aerography. Be that as it may, the predilection of these cysts for the regions of the basilar cisterns and their tendency to wind their way along the brain stem are points worthy of note when one is confronted with either a supratentorial or an infratentorial epidermoid.

SUMMARY AND CONCLUSIONS

1. A review of the literature revealed 205 cases of intracranial epidermoids.

2. Of this number, 7 instances have been recorded in which the lesion was situated in both the supratentorial and the infratentorial position, and to these the eighth example is added.

3. It is suggested that the term "cutaneous proliferating cyst" (Paget) would be an acceptable designation for the neoplasm now called epidermoid, or cholesteatoma.

PSEUDOJACKSONIAN EPILEPSY IN CHILDREN

MAJOR JOHN E. SCARFF

MEDICAL CORPS, ARMY OF THE UNITED STATES

An important advance in the treatment of so-called idiopathic epilepsy will be made if it is possible to break up the great army of epileptic persons, now regarded collectively as one group, into smaller, component groups, each with its own unique and constant clinical features, expressing its own individual etiologic mechanism and, finally, responding to its own specific method of therapy.

The first step in such a program must be the accurate description and delineation of all the various clinical syndromes as they are observed from time to time. Only after this can the etiologic factors and the appropriate therapy in any given case be determined. In 1936, in line with this thought, I described such a specific epileptic syndrome¹ which had come to my mind, and suggested a possible form of therapy. The present paper consists essentially of a description of a second specific epileptic syndrome, with an account of my experiences in attempting to determine its cause and to find a specific method of treatment. Unfortunately, these objectives have not been completely achieved, although the experiences, to date, suggest possible answers to these questions.

THE CLINICAL SYNDROME

The specific epileptic syndrome here described has been encountered only in children. The youngest child was 1½ years old when the seizures began; the oldest, 12 years of age.

The seizures are characterized by single or multiple, repeated "twitchings" or clonic "jerkings" of the extremities on one side of the body. These twitchings affect both the arm and the leg and start simultaneously in them. In sharp contradistinction to the true jacksonian seizure, they do not start from a focal point, such as the thumb or a finger or toe, and there is no "march" from one topographic cortical representation to another, which is such a fundamental characteristic of the focal convulsion as described by Hughlings Jackson; nor is there a crescendo with a peak of activity and then a falling off. The movements simply start abruptly, continue for a while with even intensity

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Scarff, J. E.: A Specific Epileptic Syndrome Relieved by Lysis of Pacchionian Granulations, *Arch. Neurol. & Psychiat.* **36**:373-375 (Aug.) 1936.

and stop. They never spread to the extremities of the opposite side, no matter how long they are sustained on the one side. Nor does the patient ever lose consciousness, bite his tongue or become incontinent.

The duration of the attacks ranges from three or five seconds to five or six minutes. The frequency of the seizures varies from two or three to as many as forty or fifty daily, but for each individual patient the frequency, once established, remains surprisingly constant day after day. Neither phenobarbital nor dilantin has any appreciable anticonvulsive effect on the seizures.

Hemiparesis on the side of the seizures developed at one time or another in each of the patients studied. The children who had right-sided paresis usually also suffered some aphasia. Psychometric tests were done on 6 of the children. The mental rating for 1 child was far below the normal level; a boy, who was very sick at the time the tests were made, was rated as normal; the remaining 5 children were given "very superior" mental ratings. The pneumoencephalograms revealed mild, diffuse cerebral hypoplasia (or atrophy) on the affected side in 6 of the 7 patients. Electroencephalograms, which were taken on 5 of the 7 children, showed a strikingly constant mixture of large, slow waves, with fast, "spiky" waves.

PATHOLOGIC DATA

The observations on cerebral exploration were inconstant, and hence disappointing. Subarachnoid fluid was excessive in 4 cases. The gyri and sulci were essentially normal in all cases. Pacchionian granulations appeared unusually dense in 4 cases. In 1 instance there was a small calcified mass of scar tissue, 1 cm. in diameter and about 1.5 cm. beneath the surface of the precentral gyrus, in the arm area of the right hemisphere.

Electrical stimulation of the cortex was performed in all 7 cases. The cortex was extremely refractory in 2 cases, gave normal focal responses in 3 cases and responded with convulsions in 2 cases when stimulation was applied in the vicinity of the particularly dense pacchionian granulations.

Electrocorticograms were made in 3 cases. These were normal in 1 instance but showed abnormal potentials in the other 2 as the superior mesial border of the hemisphere was reached.

No autopsies were performed in this group.

SURGICAL PROCEDURES AND RESULTS

No therapeutic measure was attempted on the exposed brain in cases 2 and 3, as none was indicated. In 1 of these cases the course continued to be progressively downhill, while, curiously, in the other the child made an almost complete, spontaneous recovery.

Large, dense, anomalous pacchionian granulations were divided in 4 instances (cases 1, 4, 5 and 6), the brain thus being freed of this rigid attachment along the superior mesial border of the hemisphere. The rationale exercised in this procedure is that previously described by me in 1936,¹ namely, that in brains having constitutionally low thresholds for stimulation the constant tug of unyielding pacchionian attachments between the cortex and the vault may be an irritating factor in the same manner as adhesions sufficiently strong to stimulate the production of convulsions. In each of these 4 cases the granulations were unusually dense. In cases 5 and 6 the excitability of the cortex to electrical stimulation increased notably as the region of attachment of the pacchionian granulations and the cortex was approached. In both these instances pronounced improvement in symptoms followed operation. Of the other 2 cases in which the granulations were divided, there was improvement in 1 (case 1) and a striking, progressive downhill course in the other (case 4).

In the last, but probably the most important, case of the series (case 7) a small calcified cicatrix, about 1.5 cm. in diameter, situated about 1 cm. below the surface of the precentral gyrus and close to the superior mesial border of the hemisphere, was excised. The boy has not had a single convulsion since the operation, nearly three years ago, and this in spite of the fact that he has taken no drugs for the last year. Moreover, the left hemiparesis, which was nearly complete prior to operation, has cleared up almost entirely. This boy now attends school regularly and participates freely in all sports on an equal footing with the other boys.

REPORT OF CASES

CASE 1.—J. B., a boy 4 years old, born Feb. 14, 1935, in May 1937, when he was a little over 2 years old, while suffering from a severe cold, had a generalized convulsion lasting eighteen minutes. Six months later, one year before admission, he began having seizures characterized by sudden stiffening of the body and extremities, with the head thrown back and the eyes turned to the right. These seizures occurred at first about once a month. A year later, about December 1937, the character of these seizures changed. They increased in frequency, were limited almost entirely to the right arm and leg and became more jerking and clonic in character. They lasted only a few seconds, during which time the child might be momentarily unconscious. When the seizure was over, he usually resumed his play immediately, and there never was tongue biting or incontinence. These new seizures occurred on the average of five to six times daily. Simultaneously with this change in the seizures, rapidly progressive weakness appeared in the right arm and leg and the right side of the face, and three months later aphasia developed. After a few weeks there was decided improvement in the hemiparesis and the aphasia. Gradually, however, the signs and symptoms again returned, and on Oct. 5, 1939 the child was admitted to the Neurological Institute.

Psychometric examination showed pronounced mental retardation, although the rating was probably influenced by his aphasia. Pneumoencephalograms showed slight hypoplasia of the left cerebral hemisphere.

On October 21 exploration of the left cerebral hemisphere was carried out, with the patient under anesthesia induced by avertin with amylene hydrate supplemented by a local anesthetic. There was a considerable increase in fluid in the subarachnoid space, especially as the midline was approached. The convolutions and sulci appeared to be normal. The primary motor gyrus was identified by electrical stimulation, and after this electrocorticograms were taken from many areas. From most of the exposed brain normal rhythms and potentials were obtained, but as the points studied approached the midline atypical potentials appeared, characterized by slow waves (1 to 2 per second), high potentials and sustained plateaus. In this connection, it should be observed that the avertin anesthesia had been supplanted by very light ether anesthesia for a few minutes, during the elevation of the flap; so these "plateau" waves may have been due to a residual effect of the anesthesia. On the other hand, it should be noted that these abnormal potentials were present only near the superior mesial border of the hemisphere, from areas adjacent to pacchionian granulations. These granulations were divided empirically but on the rationale that they might be acting as adhesions to make the brain locally more irritable, and a small piece of cellophane was interposed. Closure was then carried out in the usual manner.

The postoperative course was encouraging, only one attack occurring between the operation and the time of discharge from the hospital. From October 1939 until April 1940, while receiving $\frac{1}{4}$ grain (15 mg.) of phenobarbital three times a day, the boy had no attacks whatever. The phenobarbital was then discontinued, and during the next two months the patient had an average of only one attack a week, in sharp contrast to the five or six daily seizures which he had suffered before operation.

Unfortunately, in July 1940 the family moved to the Pacific coast, and contact with the child had been completely lost since then.

CASE 2.—J. K., a boy 4 years old, born in June 1936, developed normally until November 1938. When he was a little over 2 years old an unexplained fever (temperature, 106 F.) developed, during the course of which he had a generalized convulsion lasting several minutes. During the next two years he had a generalized convulsion about every three months.

On Feb. 21, 1940, however, the patient had four seizures, all confined to the right side, consisting of twitchings of the right arm and leg and the right side of the face and turning of the head to the right. These lasted from one to four minutes. Apparently, the initial movement appeared always in the thumb and index finger but spread almost instantly to involve the entire right side of the body. It could not be definitely ascertained whether or not the patient was entirely unconscious during the attacks, but it is thought not, for immediately after the seizures he would get up, rub his left eye, complain of pain in it and then resume play. After the abrupt onset of these attacks he suffered three or four seizures daily.

On April 27, 1940 the patient suddenly became worse. On that date he had fifteen right-sided seizures, similar to those described, and on the next day thirteen. Simultaneously with this exacerbation there developed severe spastic weakness of the right arm and leg, so that the child dragged his leg in getting about. During the next month these attacks continued to occur many times daily, in spite of administration of 2 to 4 grains (0.13 to 0.26 Gm.) of phenobarbital daily, and the paresis increased. On June 10 the right hand was completely paralyzed, and the right leg was held in constant spastic extension. There was considerable aphasia.

The pneumoencephalograms were normal. The electroencephalograms showed grossly pathologic high voltage, slow waves, with a frequency of 1 to 6 per second, over both hemispheres. Faster spike components, with a frequency of 10 to 20 per second, were also often observed. These spike formations were more frequently seen over the right hemisphere, while the large, slow components favored the left.

On June 13, with the child under anesthesia induced by avertin with amylene hydrate, a large osteoplastic flap was turned up on the left side. The cortex appeared normal in all respects. Cortical stimulation was carried out, with an interrupted current of 2 volts at a frequency of 60 cycles per second. Response was obtained from only a single point, and this appeared to be primarily sensory. Each time a certain point, presumably in the postcentral gyrus, was stimulated, the patient would cry out sharply and move his right hand and arm in a voluntary fashion.

Electrocorticograms were then made from forty points on the exposed cortex, which were numbered and photographed. These tracings showed diffuse electrocortical dysfunction involving the tested areas of the exposed cortex, but maximal near the superior border of the hemisphere, in what was taken to represent the primary motor area for the upper extremity.² These observations have been reported in detail in another article.³ Extirpation did not appear justified; hence the exploration was brought to a close without any therapeutic measure being carried out.

At the time of discharge from the institute, on June 23, the patient's status was essentially the same as it had been before operation; that is, he was severely hemiparetic on the right side of the body and almost totally aphasic. He was placed under treatment with phenobarbital, 0.090 Gm. daily, but during the second day at home he had seven seizures. For this reason the dose of phenobarbital was increased to 0.150 Gm. daily. During the next six to eight weeks he suffered six to eight attacks daily. After that the attacks gradually lessened in frequency and severity. From September 1940 to February 1941 he had only three seizures. At this time the amount of the drug received was reduced to 0.060 Gm. (on some days only 0.030 Gm.) daily. Between February 1941 and May 1941 he had no attacks.

I last saw this patient on Oct. 27, 1941. At this time he showed amazing and baffling improvement. Both the right hemiparesis and the aphasia had disappeared completely. He was bright, active and talkative. Since May 1941 he had been taking 0.060 Gm. of phenobarbital daily, and during this time he had not had a single convulsive episode.

CASE 3.—F. F., a boy aged 3 years 9 months, was first seen at the Neurological Institute in March 1938. He had had a normal birth and had been apparently well until November 1937, when he was about 2½ years of age. At that time there was an abrupt onset of seizures, which consisted of transient twitching of the left orbicularis palpebrarum muscle and of the left arm, lasting only two to three seconds. In the arm the movements consisted simply of sudden flexion of

2. Scarff, J. E.: Primary Cortical Centers for Movements of Upper and Lower Limbs in Man: Observations Based on Electrical Stimulation, *Arch. Neurol. & Psychiat.* **44**:243-299 (Aug.) 1940.

3. Scarff, J. E., and Rahm, W. E., Jr.: The Human Electrocorticogram, *J. Neurophysiol.* **5**:418-426 (July) 1941. (Detailed case records published with reprints.)

the fingers, wrist and elbow. These isolated jerkings recurred as often as once every twenty to thirty minutes. There was no loss of consciousness, tongue biting or incontinence during the attacks. Coincident with the onset of these seizures, there began a slowly developing spastic weakness of the left arm and leg, which caused him to drop objects from his left hand and to drag his left foot. He seemed to be unusually intelligent and likeable. Psychometric tests showed him to be of superior intelligence.

The roentgenograms were normal. The pneumoencephalogram showed slight generalized cerebral hypoplasia, possibly more pronounced on the right side. Electroencephalograms showed large, slow pathologic waves (1 to 5 per second), generally over both hemispheres, together with intermittent fast spikes (12 to 20 per second). These various pathologic components were all noticeably lateralized to the right side of the brain.

On May 25, 1939, with the patient under anesthesia induced by avertin with amylene hydrate supplemented with a local anesthetic, the right cerebral hemisphere was explored as far superiorly as the mesial border. There was more subarachnoid fluid than is normally present. Nothing else of apparent significance was noted. Electrical stimulation of the cortex was attempted with a faradic current from an induction coil, but, although a strong current was used, the entire hemisphere was extremely refractory and only one motor point, that for the fingers, could be identified. Electrocorticograms were not being made at this time. Since exploration had yielded no indication for further procedure, closure was made.

The immediate postoperative convalescence was uncomplicated, and the child was discharged on June 6, 1939, with instructions to take 0.030 Gm. of phenobarbital three times a day. Under this therapy, the attacks occurred with the same frequency and severity (at times every twenty minutes) as they had previous to the operation without the drug. Accordingly, in April 1940 phenobarbital was discontinued and dilantin, 0.1 Gm. twice a day, was substituted. After this the patient improved somewhat. He was last seen in April 1941, at which time he was having attacks similar to those previously suffered, but occurring never more than three times a day and often not at all for a week or two. The paresis, however, had slowly progressed. The entire left side of the body was hypoplastic and spastic. The arm was held flexed at the elbow and wrist, with marked loss of power. The leg was much less involved. Curiously, though, there was transient clonus of both legs, with a persistent Babinski sign on the left and an equivocal one on the right.

CASE 4.—L. R., a boy 4 years old, had an unexplained fever (temperature of 102 F.) in March 1939, without apparent immediate sequelae. In June 1939 he suddenly began to have spells characterized by pain in the arm, followed almost immediately by extension of the right arm and the right leg, occasionally accompanied by a few mild clonic movements. The child fell but did not lose consciousness and usually cried. Such an attack lasted about five to ten seconds. When the extremities relaxed, the child would stop crying and say, "I feel okay now," and resume his play. The entire episode required about fifteen to twenty-five seconds. These attacks occurred about six times daily.

When he was first admitted to the Neurological Institute there was no paresis of the affected side and the reflexes were essentially normal, both before and immediately after an attack. But after about ten days there appeared slight weakness of both the right arm and the right leg, and this increased rapidly into pronounced right spastic hemiparesis. Psychometric tests gave the child a very superior rating.

Roentgenograms of the skull were normal. Pneumoencephalograms revealed slight hypoplasia of the left cerebral hemisphere. Electroencephalograms suggested a convulsive disorder with a focus in the right frontal and motor region, more frontal than motor.

A right craniotomy was performed on July 26, 1939, with the patient under anesthesia induced by avertin with amylene hydrate supplemented by a local anesthetic. The exposed cortex was hyperemic; the gyri were narrow and the sulci widened. There were lakes of cerebrospinal fluid between many of the gyri. Cortical stimulation was carried out with faradic current, and the primary motor areas for the upper extremity were identified. Electrocuticograms taken from these varied points were essentially normal. Unusually dense pacchionian granulations were present along the superior mesial border of the hemisphere, both in the superior portion of area 6 α - β and posteriorly in area 5, and these were divided, for reasons which will be discussed elsewhere.

The immediate postoperative course was uncomplicated, but there continued to be steadily progressive right hemiparesis, which at the time of his discharge, on August 12, was pronounced. He was still having five to ten right-sided seizures daily.

The patient was seen on Nov. 20, 1940, at which time he had almost an athetosis of the right arm and hand, and when he walked he lifted his right leg high and slapped his foot, flail-like, to the ground. He was fairly bright. He had been taking phenobarbital, 0.030 Gm. three times a day, under which regimen he had had no convulsive seizures during the daytime for eight months, although he was having some at night.

The child was last seen on April 17, 1941. At that time he was suffering from right hemiparesis with severe spasticity and, in addition, was beginning to experience transient spastic states in the left arm and leg. He was unable to stand or even sit alone. He appeared doped and would have fallen off his chair had he not been supported by his mother. These findings suggested progressive, bilateral, degenerative disease of the brain, or possibly some rare neoplasm. The mother was advised to bring the child for further studies, to include pneumoencephalographic examination, but she refused. She has also refused to bring the child back to the clinic for reexamination.

CASE 5.—E. M., a girl 7 years old, born in January 1932, was apparently well until November 1937, when she was 5 years old. At that time she had a generalized convulsion while at school. Seizures were present intermittently for four and a half hours. The patient was unconscious during this time. After the general seizure ceased, twitchings of the right side of the face persisted for some time. After this episode, the patient was well for ten months, until Aug. 6, 1938, when she was awakened from a sound sleep with "twitchings" of the right arm and leg, which lasted for five minutes. These recurred at frequent intervals during the next twelve hours and thereafter with decreasing frequency during the next seven to eight days, after which the patient again seemed well. However, in October 1938 she began to experience "twitchings" of the right leg below the knee, lasting two to three minutes and recurring three to four times daily.

By April 1939 these spells had increased greatly both in severity and in frequency. The "shaking" spells had originally involved only the leg, but now affected also the arm. They lasted five to six minutes at a time and were so violent as to make the bed shake. During all of this time the left side of the body remained entirely unaffected; there was no incontinence, and the patient remained entirely conscious throughout. These shaking spells recurred almost continuously, with only a few minutes between them, for four to six days at a stretch, and then the

patient might have none at all for seven to fourteen days. Lately, between attacks, there had been isolated, single simultaneous twitchings of the right arm and the right leg. Phenobarbital, 0.03 Gm. three times a day; calcium lactate, 0.6 Gm., and a high fat and low fluid diet were all tried, but this situation had obtained without much variation for six to eight months, when she was finally admitted to the Neurological Institute on April 13, 1939.

Since November 1938 the parents had noticed an increasing tendency to drag the right leg in walking and to stumble. There appeared to be no weakness of the upper extremity. After attacks, however, speech was often confused and unintelligible.

The results of neurologic examination were entirely normal except for ankle clonus on the right side. There were normal plantar responses bilaterally. The child was pleasant, and psychometric tests revealed normal intelligence for her age.

Pneumoencephalograms revealed a moderate degree of cerebral hypoplasia, more pronounced on the left. Electroencephalograms were characterized by extremely large, pathologic slow waves, at a rate of about 2 per second, appearing generally over both hemispheres but distinctly lateralized to the left. On the left side these slow waves showed foci ranging anteroposteriorly from the postcentral area into the anterior portion of the frontal lobe; they were larger over these regions than more posteriorly, over the occipital lobe and the parieto-occipital area. Along with the slow delta waves, a spike component was often noted, resulting intermittently in large wave-spike contours. The pattern indicated diffuse cortical involvement, much more extensive on the left side.

On April 15 exploration of the left cerebral hemisphere was performed with the patient under anesthesia induced by avertin with amylene hydrate supplemented with a local anesthetic. There was slightly more subarachnoid fluid than is usually seen at operation, but the gyri and sulci appeared normal. The entire superior mesial border of the hemisphere was involved, with an unusually dense plexus of veins passing into the superior longitudinal sinus, and these, in turn, were bound up in peculiarly dense paccchionian granulations. Stimulation of the cortex with weak currents obtained from the thyratron stimulation produced isolated movements from the various primary motor areas of the upper extremity, but as the superior mesial border of the hemisphere and the dense paccchionian granulations associated with it were approached, stimulation at various points with even a weak current produced abrupt, powerful mass movements of the entire lower extremity, suggesting movements which the limb might assume in locomotion. This region appeared hyperirritable to stimuli, and on the chance that the dense attachments between cortex and dura afforded by the paccchionian granulations might be contributing to this irritability, I divided them and interposed a small piece of cellophane between the divided ends of the veins and granulations. Closure was then made in the usual manner.

The postoperative course was uncomplicated. The child was placed under treatment with phenobarbital, 0.015 Gm. three times a day. At the time of discharge she seemed definitely better than before operation. There was a progressive reduction in the number of "twitchings" of the right leg, and for five days prior to discharge there had been none at all. The gait, too, was much improved, and the spasticity of the right leg appeared to be much less than before operation. There was, however, very slight twitching of the right side of the mouth. She was last seen on April 29, 1940, about one year after operation. At that time she was still taking phenobarbital, the same dose as before. During the year just ending she had had seizures similar to her severe preoperative attacks on

only two occasions. In October 1939 seizures occurred during a period of about a week, gradually subsiding spontaneously. About April 10, 1940, she had several attacks during a three day period, but these were mild. She was still bothered by momentary, single "ticlike" twitchings of the left eyelid, but on the whole she was much better than she was before operation.

CASE 6.—J. T., a girl aged 19 years, was admitted to the Neurological Institute in May 1939, complaining of seizures involving the right side. In 1932, when 12 years old, she began to experience episodes during which she suddenly became inattentive and unresponsive, usually with simultaneous twitching of the right leg and arm. Sometimes there was almost no twitching; at other times there were rather severe jerking movements, involving the face as well as the arm and leg. As a rule, these attacks lasted twenty to thirty seconds; the left side of the body was not involved, and the patient did not lose consciousness. These attacks recurred four to eight times during twenty-four hours, or several weeks might pass without them. In addition to these attacks, since 1934 the patient had had each year from one to three true jacksonian convulsions, starting with coarse, clonic movements in the right arm and spreading in typical fashion to the right leg, accompanied by loss of consciousness, incontinence and biting of the tongue. During the past year she had been receiving dilantin, 1 capsule (0.1 Gm.) three times a day, and phenobarbital, 0.06 Gm. three times a day.

Examination at the time of admission revealed nothing abnormal except for slight hyperreflexia and a Babinski sign and slight reduction of stereognostic sense on the right side. The patient was naturally left handed. Psychometric tests showed her to be of very superior intelligence. Pneumoencephalograms revealed mild cerebral hypoplasia on the right (!) side.⁴

On June 8, 1939, with the use of local anesthesia, extensive exploration of the left cerebral hemisphere was performed. The gyri and sulci appeared to be normal; there was no excess of subarachnoid fluid.

Electrical stimulation with the thyatron gave sharply focal responses along the motor gyrus, which was easily identified throughout its length. At the junction of the precentral and postcentral gyri with the superior mesial border of the hemisphere there were unusually large, dense pacchionian granulations accompanying a plexus of veins, which were remarkably large and numerous. Electrical stimulation with weak current at the superior border of the hemisphere produced a generalized convulsion, beginning with abduction of the arm and subsequently resembling somewhat the pattern of the clinical seizures seen before operation. Because the clinical evidence pointed to this region and the pacchionian granulations lay in an anatomically acceptable area and, finally, because stimulation at this point produced the only convulsion obtained, and one which did, in fact, resemble somewhat the preoperative clinical seizures, it was felt that there were sufficient indications for dividing these granulations. Accordingly, this was done, and the divided ends were separated with Cargyle membrane. Closure was then made in the usual manner.

The postoperative convalescence was uneventful, and the patient was discharged on June 21. She was last seen on May 25, 1941, almost two years after operation. During the six months just ended she had been taking dilantin, 1 capsule three times a day, and phenobarbital, 0.030 Gm. twice a day, somewhat less medication

4. Casamajor, L.; Smith, J. R.; Constable, K., and Walter, C. W. P.: The Electroencephalogram of Children with Focal Convulsive Seizures, *Arch. Neurol. & Psychiat.* **45**:834-847 (May) 1941.

than she had received preoperatively. She had experienced none of the severe jacksonian seizures with loss of consciousness since her operation two years before, and the minor twitching episodes of the right arm and leg had been greatly reduced in severity and decreased to one-half their former frequency.

CASE 7.—R. G., a boy 8 years old, was admitted to the Neurological Institute in May 1939. At the age of 17 months he began to have tremors and jerking movements of the left arm, which lasted for only a few seconds. The spells recurred without change from the time the patient was 17 months until he was 5 years old. At the age of 5, however, the left leg stiffened each time the arm jerked. There was never any loss of consciousness. These seizures lasted for only a second or two. They might occur two to three times a day, or several weeks might pass without any attacks. During all this time the patient was receiving systematic phenobarbital therapy, under a physician's direction, without apparent relief.

Weakness of the left arm and hand was also noticed by the mother at the same time that the aforescribed jerking first appeared. No weakness of the left

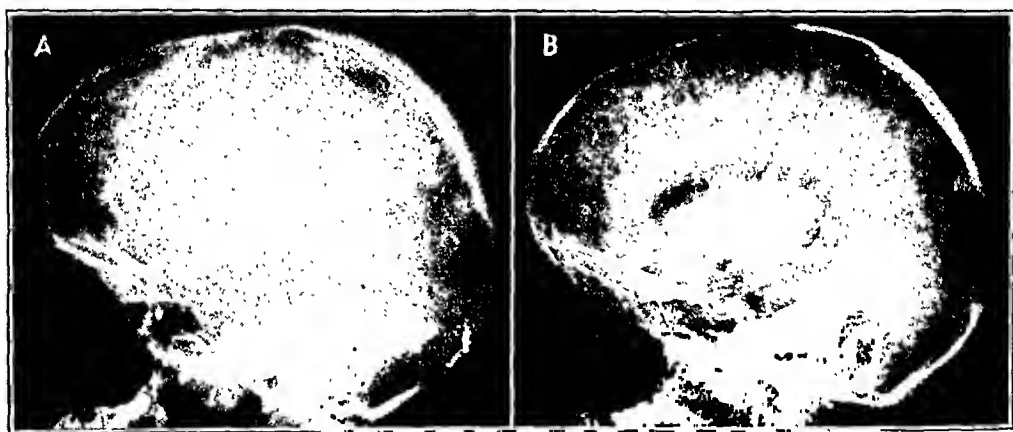


Fig. 1 (case 7).—*A*, preoperative roentgenogram of the skull, showing the position of the calcified subcortical cicatrix, about 1.5 cm. beneath the surface of the brain and about 1.5 cm. from the midline. The patient, a 12 year old boy, had had convulsions since he was 1½ years old. *B*, preoperative pneumoencephalogram. Note how the roof of the lateral ventricle has been pulled upward by the calcified subcortical cicatrix. In addition to the convulsions, severe, progressive left hemiparesis was developing prior to operation.

leg was noted at that time, but when the boy first began to walk, at 17 months of age, it was observed that he dragged his left leg.

The conditions just described persisted without essential change in character or degree until October 1938, seven months before the present hospitalization, when the patient was approximately 7½ years old. At that time, however, the character of the spells changed drastically. In these new spells the patient first lost consciousness and the body stiffened; the head turned to the right; the right side of the face started to contract, and the right arm was abducted. In short, there occurred a typical jacksonian seizure followed by generalized convulsions. From October 1938 until May 8, 1939 this boy had had three or four such attacks daily.

Simultaneously with the increase in severity of the attacks, there occurred a decided increase in the left hemiparesis. When admitted, the patient could hold nothing in his left hand and could not bear any weight on his left foot, but dragged it behind him. Psychometric tests showed that the patient functioned at a low average mental level despite his great physical disability.

Electroencephalograms revealed abnormal, large, slow waves, with a rate of 2 to 6 per second, together with wave-spike contours, with a frequency of 2 to 3 per second, over the central and postcentral areas of the right cerebral hemisphere and, to a lesser degree, over a similar portion of the opposite hemisphere.

Plain roentgenograms of the skull showed a small deposit of calcium, about 1 cm. in diameter, in the right central region, about 1 to 2 cm. to the right of the midline and about 1 to 2 cm. below the surface of the cortex (fig. 1). The pneumoencephalograms showed an outpouching of the right ventricle toward the region of the calcific deposit just referred to, which indicated that the latter was a scar.

On June 19, 1939 a right parietal craniotomy was performed, the primary motor gyrus incised and a subcortical, calcified cicatrix removed. By precise

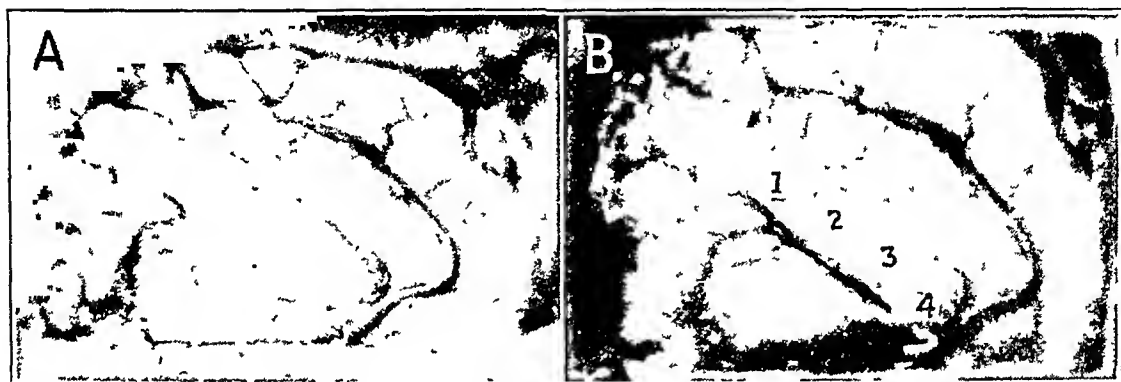


Fig. 2 (case 7).—*A*, the normal-appearing right cerebral cortex as first exposed at the operating table (retouched). *B*, the same area after excision of a calcified subcortical cicatrix (retouched). The numbers indicate primary motor points for the upper extremity as identified by electrical stimulation. The dark line anterior and parallel to the numbers is the incision in the cortex through which the cicatrix was removed.

measurements from suture lines, as revealed in the roentgenograms, and on the skull itself, a point on the surface of the brain was determined which, it was felt, was situated directly over the calcific deposit seen in the roentgenograms. Electrical stimulation of the cortex then revealed that the point lay directly on the primary motor gyrus in the hand area. With considerable trepidation this gyrus was incised lengthwise for a distance of 2 to 3 cm. and to a depth of 2 to 3 cm. Here I found a firm, irregular, calcified cicatrix, which I removed.

The immediate postoperative course was fairly smooth, and the patient was discharged on the thirteenth day. He has had no attacks of any sort during the nearly three years since the operation, in spite of the fact that he long ago stopped taking any medicament. In addition, there has been an entirely unexpected and considerable improvement in motor power and general use of his left arm and leg. His mother states that he is constantly on the go and that he is able to "lick both of his brothers at either wrestling or fighting."

COMMENT

The primary purpose of this paper has been to describe for the first time a second ¹ specific epileptic syndrome thus far observed only in children. To facilitate and provoke discussion, I have called it "pseudojacksonian" epilepsy of childhood.

The cause and the pathologic mechanisms behind the clinical syndrome, unfortunately, are not yet clear. Experience with these cases, however, suggests two mechanisms for consideration. The first is that anomalous pacchionian granulations may produce irritation of a brain with a constitutionally low threshold somewhat as do adhesions, thus acting as a "secondary trigger mechanism" in releasing convulsive phenomena.¹ This was the working hypothesis utilized in management of some of the earlier cases in the present series.

The simultaneous and equal involvement of the arm and the leg on one side in rhythmic, repetitious and sometimes well sustained movements early suggested to me that these movements might represent fragments of some more complex action pattern having to do with locomotion, possibly even a vestige of a phylogenetically earlier manner of propulsion, such as quadrupedal walking or swimming.

The Vogts, in 1926, pointed out that strong stimulation of area 6 a β , near the superior mesial border of the hemisphere, would result in simultaneous mass movements of the two opposite extremities, and Foerster, in 1936, reported similar mass movements resulting from stimulating the superior border of the hemisphere not only anterior to the central sulcus (area 6 a β) but posterior to it (area 5). Both of these areas, it will be noted, are the regions where the larger pacchionian granulations are located.

If anomalous pacchionian granulations were to provide irritative stimuli to the brain, it is evident from the foregoing discussion that the irritation might easily fall on area 6 a β or area 5 and thus set off the mass movement of the contralateral arm and leg, described by Vogt and Vogt in animals and by Foerster in man. Under these circumstances, lysis of the granulation, with release of the brain, might remove the irritative stimuli to the brain which were causing these movements. It was this reasoning which led me to divide the pacchionian granulations in 4 of the cases.

The results of dividing the pacchionian granulations gave some support to the aforestated thesis. In 3 of the 4 cases in which this treatment was employed there was definite improvement, and this was most evident in the 2 cases in which electrical stimulation of the cortex revealed hyperirritability in the region of the granulation and in which the electrocorticograms showed dysfunction. In the fourth case, in

which division of the granulations failed to result in improvement, there had been no indication for the division other than the appearance of the granulations.

A second mechanism is suggested in the last case (case 7). Here I was fortunate in having the identity and the precise location of the etiologic factor, a subcortical cicatrix, revealed in the roentgenogram, since the lesion was calcified. It is highly significant that this cicatrix was close to the area held under suspicion during my long struggle with the first 6 cases, namely, the region close to the superior mesial border of the hemisphere and to the primary motor cortex.

It is important to note that this lesion was entirely below the surface layers of the cortex. Whatever the pathologic and physiologic significance of this may be, its clinical and surgical significance is great, for this type of lesion would never be found by inspection of the exposed brain alone.

The results of treatment in case 7 were so strikingly successful that it is evident that this case probably holds the key to the specific treatment of this particular syndrome. Although one can only speculate, it seems likely that a similar cicatrix was the basic etiologic factor in the 5 preceding cases (except case 4), the lesion being missed because it was not calcified. If this is true, then the role of the pacchionian granulations was simply one of tugging on and irritating the brain at a point where it had already become locally hyperirritable owing to the presence of an active subcortical cicatrix, and they thus served as secondary activating mechanism. Technical problems are inherent in the fact that the lesion is subcortical. It is probable that the seat will have to be sought for at the operating table with a bipolar electrocorticograph, much as one seeks metal buried beneath the ground with electromagnetic indicators.

There remains the final question as to the origin of the cicatrix itself. Unfortunately, on this point I have no data, or even good speculations. The physiologic effect of the cicatrix is worth a few words, however. It should be noted that the boy in case 7 had almost complete hemiparesis before operation. Despite the trauma incident to a longitudinal incision, $\frac{1}{2}$ inch (1.27 cm.) long and $1\frac{1}{2}$ inches (3.8 cm.) deep, splitting the primary motor gyrus, plus the trauma incident to the excision of the irregular cicatrix, the hemiparesis cleared up almost completely after the cicatrix was removed. I can explain this only by assuming that the scar must have been constantly irritating and have produced some edema about it, which impeded the function of the affected area of the brain, much as occurs with a glioma. With the removal of the irritating lesion the edema subsided and the surrounding brain could function normally.

SUMMARY

An apparently specific epileptic syndrome occurring in children is described. It consists of repeated clonic jerkings of the extremities of one side of the body, starting abruptly and simultaneously in the arm and the leg, without "march" or loss of consciousness. The attacks occur with a rather constant frequency in each case, several to many times daily.

Hemiparesis on the side of the seizures developed at one time or another in each of the cases studied.

Pneumoencephalograms revealed mild diffuse hypoplasia of the affected brain in 6 of 7 cases. In 1 case a subcortical calcified, degenerated area was revealed. Pacchionian granulations appeared unusually dense in 4 cases.

Treatment with phenobarbital or dilantin was usually without effect on the seizures.

Lysis of the abnormal pacchionian granulations produced decided improvement in 3 of 4 cases, and removal of the calcified mass gave relief from both seizures and hemiparesis in another case.

Dr. Byron Stookey gave permission to use case material from the neurosurgical service of the Neurological Institute and assisted in the preparation of this manuscript.

Neurological Institute of New York.

MIDBRAIN DEAFNESS

TUMOR OF THE MIDBRAIN PRODUCING SUDDEN AND COMPLETE DEAFNESS

PAUL SLOANE, M.D.

A. PERSKY, M.D.

AND

M. SALTZMAN, M.D.

PHILADELPHIA

The following case of tumor of the midbrain is reported because it presented an unusual symptom, namely, sudden and complete deafness. Not many reports of this condition have appeared in the literature, and since the disorder is uncommon enough to be overlooked, even in the presence of other localizing signs of a lesion of the midbrain, the report of a single case seems warranted. Neighborhood symptoms, such as hypersomnolence, mental changes and palatal paralysis, were also present, but were not sufficiently outstanding to require special mention, particularly since their significance is well recognized.

REPORT OF A CASE

History.—C. R., a white man aged 55, was admitted to the Mount Sinai Hospital on Oct. 11, 1940 with a history of impairment of hearing of eighteen months' duration. At the time of the onset it was said that he complained of weakness and pain in the legs. There had also been increasing loss of sexual potency. The patient was nevertheless able to carry on his daily occupation until about two weeks prior to admission. At that time his wife noticed that he slept most of the time and that it was difficult to arouse him.

One of us (M.S.) had been treating the patient at various intervals for impairment of hearing. It was found that the drums were retracted and that catheterization of the eustachian tubes afforded the patient some relief from his "stuffed head." The deafness, however, was not of the conduction type, and nasopharyngoscopy and diagnostic catheterization disclosed no abnormalities about the eustachian tubes. An audiometer test done one week prior to admission showed a hearing loss of 40 to 60 decibels at the higher tone levels, whereas the impairment in the lower tone range was only 20 to 30 decibels. It was evident that the neural mechanism of hearing was definitely at fault. The vestibular nerve, however, appeared not to be involved. As the patient's history disclosed that he had been imbibing considerable quantities of bootleg alcohol, the possibility of toxic neuritis of the cochlea was considered, and a preparation of the vitamin B complex was prescribed. When the patient, however, suffered sudden complete

From the Neurologic and Otolaryngologic Departments, Mount Sinai Hospital.

loss of hearing and nystagmoid movements of the eyes were noted, an organic lesion of the brain was suspected, and the patient was admitted to the Mount Sinai Hospital for study.

Examination.—On admission the patient seemed to be resting comfortably and offered no subjective complaints. The drowsiness described by his wife was not observed at this time. The temperature, pulse and respiration were normal. The pupils were round, equal and regular; they reacted sluggishly to light and better in accommodation. The extraocular movements were normal. There were a few nystagmoid jerks during rotation of the eyes in all directions. Hearing was lost to both high and low notes, and there was absence of bone conduction bilaterally. The audiometer test revealed complete loss of hearing in both ears. External examination of the ears demonstrated old tubal catarrh, which was considered insufficient to account for the deafness. There was drooping of the right side of the soft palate, and the gag reflex was absent bilaterally. Both knee jerks were absent. The bladder was distended.

Two days later the patient's cerebation was found to be slow and out of proportion to the degree of his deafness. At this time the pupils were unequal, the right being larger than the left. Neither pupil reacted to light or on convergence. Spinal tap disclosed a pressure of 130 mm. of water. A Bárány examination was attempted but was unsuccessful because of the patient's mental hebetude.

Course of Illness.—Within a week the mental dulness had progressed to a state of complete stupor with incontinence. It was difficult to arouse the patient for his meals, but when he was finally awakened he seemed to be alert and cooperative. A few days later, however, his responses became irrelevant, and he seemed to be confused. He tended to persevere and had no recollection of recent events. He was also abusive toward his wife. Dehydration by intravenous injection of sucrose was tried but had no effect on the patient's mental state. The fundi remained normal, and there was no increase of intracranial pressure on repetition of the spinal tap. At this time, weakness of the right arm was noticed, and the deep reflexes in this limb were increased.

Results of examination of the blood, urine and spinal fluid were without significance. Roentgen studies of the chest, mastoids and skull also failed to reveal any evidence of abnormality.

The patient's coma increased, and pulmonary edema developed, of which he died on October 28, seventeen days after admission.

Autopsy.—Autopsy, performed by Dr. David R. Meranze, pathologist to the Mount Sinai Hospital, revealed the following changes: moderate aortic atheroma, slight diffuse dilatation of the heart with fiber atrophy, marked passive congestion and focal edema of the lungs, congestion of the spleen with focal hemorrhage, cloudy swelling of the liver, subacute hemorrhagic cystitis and pronounced congestion of the kidneys.

Aside from the presence of a neoplasm in the brain stem, the brain showed no abnormalities. The tumor extended from the posterior part of the hypothalamus, and infiltrated the midbrain and pons, its tail projecting between the cerebellar hemispheres, hollowing out a shallow indentation in both hemispheres and compressing the dorsal aspect of the medulla. The tumor involved the entire tegmentum of the midbrain and pons, particularly on the left side. The aqueduct of Sylvius was displaced toward the right side without being blocked, so that it was possible to pass a probe through its entire length.

The microscopic examination of the tumor was made by Dr. Charles Davison, neuropathologist of Montefiore Hospital.

Sections of the hypothalamus, cerebellum and spinal cord were stained by the myelin sheath and hematoxylin-eosin methods. The myelin sheath preparations could not be made out well, as the paraffin sections did not take the stain well.

Hypothalamus.—There was a fairly large tumor mass, which had a varied histologic picture. With low magnification, clusters of cells having a slight papillomatous appearance were seen surrounding free spaces or blood channels, the cells being arranged in a radiating fashion. With higher magnification, the cells around these vascular channels appeared to consist of irregularly shaped, densely stained nuclei, with little cytoplasm. An occasional mitotic figure was noted. Between these dense collections of cells there was a looser tissue in which the cells consisted essentially of fibrillary astrocytes. An occasional protoplasmic astrocyte was also observed. In other regions there were a few strands of polar spongioblasts, which had a slight palisade arrangement. In still other regions there were cells with densely packed, deeply stained, irregularly shaped nuclei and little cytoplasm. Some of these could be identified as ependymal cells. Among these were also mitotic figures. The prevailing cells throughout the tumor, however, were fibrillary astrocytes.

Microscopic Diagnosis.—The diagnosis was mixed glioma, essentially astrocytoma or astroblastoma.

The diagnosis of astrocytoma was made essentially because of the numerous fibrillary astrocytes. The possibility of an astroblastoma was considered because of the arrangement of cells around the free spaces, but this could not be confirmed since no Cajal stains were made. In addition to the aforementioned glia cells there were spongioblasts, ependymal cells and atypical glia cells.

COMMENT

The outstanding feature of the case was the sudden onset of deafness in a man who had previously shown mild impairment of hearing. After otogenic causes had been ruled out, it was natural to assume that the condition was caused by involvement of the acoustic nerve. The association of fixed pupils and absence of knee jerks suggested syphilis of the central nervous system (tabes), but the results of serologic studies were negative. A lesion of the pons involving both trapezoid bodies was also suggested, but it was only after the patient began to show other evidences of cerebral involvement that the cause of the deafness was sought elsewhere.

As is well known, lesions which produce deafness as a rule involve the eighth nerve or its terminal filaments (Wilson¹). It is less well known, however, that impairment of hearing may occur with lesions

1. Wilson, S. A. K.: *Neurology*, Baltimore, Williams & Wilkins Company, 1940, vol. 1, p. 410.

of the brain stem. In the pons, for instance, it may result from involvement of the trapezoid bodies. The impairment in cases of such a lesion is more likely to be unilateral and incomplete, because the size of the pons enables many fibers to escape compression. Horrax,² in a study of 15 cases of pontile tumor, found severe bilateral impairment in 3 cases, unilateral deafness in 4 cases and questionable impairment in 1 case.

In contrast to these observations, Brunner, in his monograph,³ described the syndrome of midbrain deafness in considerable detail and concluded that tumors of the tegmentum of the midbrain are more likely to give rise to sudden and complete deafness. This is due to the fact that the auditory pathways in this region, namely, the lateral lemnisci, the posterior colliculi, the brachia of the posterior quadrigeminate bodies and the medial geniculate bodies, are closely placed together in what has been described as the "isthmus acusticus." Such lesions are usually associated with descending degeneration in the cochlear system down to the spiral nerve of the cochlea. Moreover, the small size of the midbrain and the compactness of its tissues enable a tumor of moderate size to compress the auditory pathways on both sides, as well as to produce widespread functional disorder of other systems. According to Brunner, deafness due to a lesion in the midbrain is usually a late symptom and therefore has an unfavorable prognostic significance. As a rule, it shows an unusually rapid, almost apoplectiform, progression and is associated with marked shortening of bone conduction and labyrinthine hyperexcitability. He expressed the opinion that the latter change is important in the differential diagnosis of tumors of the midbrain and those occurring lower in the brain stem or in the cerebellum. In the latter areas there is early destruction of the secondary pathways of the vestibular nerves, so that diminished excitability of the labyrinth may be observed before there is any definite impairment of hearing. One-sided lesions give rise to contralateral deafness, since the pathways on each side are connected with the opposite ear. Brunner classified the various conditions which give rise to the syndrome as follows: (1) tumors of the tegmentum of the midbrain, caudal to the red nucleus; (2) tumors of the transition zone between the thalamus and the midbrain; (3) pinealomas; (4) suprasellar tumors, and (5) tumors of the quadrigeminate plate.

In the first of Brunner's cases, that of a woman aged 36, a tumor was observed occupying the posterior portion of the right thalamus and

2. Horrax, G.: Differential Diagnosis of Tumors Primarily Pineal and Primarily Pontile, *Arch. Neurol. & Psychiat.* **17**:179 (Feb.) 1927.

3. Brunner, H.: *Otologische Diagnostik der Hirntumoren*, Berlin, Urban & Schwarzenberg, 1936, chaps. 8 and 9.

infiltrating the right cerebral hemisphere, on the one hand, and the tegmentum of the midbrain, on the other. Clinically the patient presented the symptoms of drowsiness, pathologic attacks of sleep, flushing of the face, fixation of the pupils to light, paralysis of upward gaze, cerebellar signs, increased intracranial pressure, tinnitus and severe bilateral deafness, which came on rapidly within the space of ten days. Both labyrinths were found to be hyperexcitable.

In his second case a man of 30 presented inequality of the pupils with fixation to light, limitation of upward gaze, cerebellar signs, papilledema with secondary optic nerve atrophy, signs of increased intracranial pressure, left-sided deafness with subjective tinnitus and prompt response of the labyrinth to caloric stimulation. At autopsy a pinealoma was observed which filled the posterior portion of the third ventricle and infiltrated the quadrigeminate plate and the tegmentum of the midbrain. The left cochlear nerve showed degenerative atrophy, while the right one was normal.

In Siebenmann's⁴ case a youth of 18 had a large gliosarcoma of the pineal gland, which had infiltrated the entire quadrigeminate plate, the tegmentum of the midbrain, the posterior portion of the third ventricle, the entire posterior half of the right pulvinar and the anterior portion of the cerebellum. The illness lasted twenty months. Five months after the onset the patient began to complain simultaneously of bilateral tinnitus and impairment of hearing. Hearing failed rapidly, so that one month later he was completely deaf. He also showed beginning optic nerve atrophy with diminished vision, complete paralysis of the extraocular muscles (exclusive of the rectus internus and rectus externus), accommodation paralysis of both pupils, anisocoria, lack of response to light, slowness of speech and apathy. There was loss of bone conduction, while air conduction was still present. Later air conduction was also lost. The microscopic studies in this case revealed that the primary cochlear nuclei and cochlear nerves on both sides were normal. Siebenmann stated that diminution of hearing could be ascribed to a tumor of the midbrain if (1) the deafness occurred together with other cerebral symptoms related to the tumor and (2) if the deafness showed a strikingly progressive character.

Siebenmann also summarized a number of similar cases previously reported in the literature. In all of them deafness became complete within four to eight months after it was first observed. Some of the other symptoms described in these cases were epileptic seizures, ataxia, speech disturbances, incontinence of urine, apathy, stupor, excitement, destructi-

4. Siebermann, F.: Ueber die zentrale Hörbahn und über ihre Schädigung durch Geschwülste des Mittelhirns speciell der Vierhügelgegend und der Haube, *Ztschr. f. Ohrenh.* 29:28, 1896.

bility, amnesia and depression. In addition, hydrocephalus and evidences of increased intracranial pressure usually occurred early as the result of obstruction of the aqueduct. Pupillary changes and extraocular muscle palsies were frequently present, while tinnitus occurred but was not the rule.

Weinland's ⁵ case was that of a man of 25 whose illness lasted two years. Twenty months after the onset there was pronounced impairment of hearing on the right side, papilledema with beginning optic nerve atrophy, anisocoria, sluggish reaction of the pupils in accommodation, slow and difficult speech, amnesia and depression. Section revealed a glioma, the size of a walnut, situated over the left half of the quadrigeminate plate. The lateral lemniscus had entirely disappeared in the region of the left quadrigeminate plate and showed definite degeneration in the proximal portion of the pons. There was also round cell infiltration of both acoustic nerves.

Horrax and Bailey ⁶ found that in 5 out of 12 cases of tumor of the pineal body some degree of central deafness was present, being complete in 3 cases. They ascribed it to pressure on the inferior colliculi.

In the case of Harris and Cairns,⁷ that of a young man of 20 with a pineal tumor, marked impairment of hearing developed on the left side twelve months after the onset of symptoms. This cleared up after removal of the tumor. They also ascribed the deafness to compression of the posterior quadrigeminate bodies.

The condition of the pupils in our case was the only localizing sign directly referable to the midbrain. On admission both pupils reacted sluggishly to light and better on convergence, and within a few days they became unequal and fixed. The absence of increased intracranial pressure was surprising, since it is well known that with tumors of the midbrain there is early blocking of the iter, with production of obstructive hydrocephalus. The absence in our case can be explained by the fact that the tumor had merely displaced the aqueduct to the right, without encroaching on its lumen, so that the occlusion was not complete. Thus, a probe could easily be inserted the entire length of the aqueduct. The evidences of bulbar involvement, namely, weakness of the palate and dysphagia, were apparently due to involvement of the bulbar nuclei by compression of the dorsal aspect of the medulla.

5. Weinland, E.: Ueber einen Tumor der Vierhügelgegend und über die Beziehungen der hinteren Vierhügel zu Geistesstörungen, *Arch. f. Psychiat.* **26**:363, 1894.

6. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, *Arch. Neurol. & Psychiat.* **13**:423 (April) 1925.

7. Harris, W., and Cairns, H.: Diagnosis and Treatment of Pineal Tumors, *Lancet* **1**:3, 1932.

SUMMARY

A case is reported of sudden and complete deafness resulting from a glioma which infiltrated the tegmentum of the midbrain. The other localizing signs were the presence of sluggishly reacting pupils, which later became unequal and fixed, and pathologic drowsiness and mental symptoms resulting from involvement of the hypothalamus. In addition, extension of the tumor to the medulla gave rise to weakness of the soft palate and dysphagia. An unusual feature of the case was the absence of increased intracranial pressure. This was explained by incomplete occlusion of the aqueduct of Sylvius.

269 South Nineteenth Street.

1723 Pine Street.

529 Snyder Avenue.

ATYPICAL SEIZURES ELICITED BY ELECTRICAL STIMULATION OF THE CEREBRUM IN THE CAT

J. THOMAS PAYNE, M.D.

SAM L. CLARK, M.D., PH.D.

JAMES W. WARD, M.D., PH.D.

AND

FREDERIC E. COWDEN, M.D.

NASHVILLE, TENN.

Since the pioneer work of Fritsch and Hitzig¹ in 1870 and of Ferrier² in 1873, many investigators have stimulated the cerebral cortex of animals and of man. Most such experiments have been carried out with the brain exposed and the subject anesthetized, at least lightly, or controlled with local anesthesia. Talbert,³ in 1899, using a method and (according to a recent personal communication) the very electrodes devised by Ewald,⁴ reported the results of stimulation of the cortex of unanesthetized and unrestrained animals in whose skulls were implanted permanent electrodes. It is surprising that Talbert's work was for so long a time unappreciated, since work in this laboratory for several years⁵ has indicated the value of implanted electrodes in cortical stimulation.

From the Department of Anatomy, Vanderbilt University School of Medicine.

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Convulsions elicited in unanesthetized and unrestrained animals by electrical stimulation of fixed cortical points⁶ were similar to jacksonian epileptic attacks in man. The animals exhibited rapid clonic movements of the extremities, which came in a definite order or march and were accompanied by evidence of visceral involvement. For a short time afterward the placing reactions were reduced or absent, in a manner comparable perhaps to the postseizure occurrence of the Babinski response as observed in man (Notkin, Coombs and Pike⁷). The extent of the convulsions and the pattern depended on the location of the electrode and the strength and the duration of the stimulus employed. Of some significance is the fact that the convulsions could be repeated from day to day in the same animal.

In several instances in the experiments described by Ward and Clark⁶ an unexpected variation of the typical jacksonian seizure was observed (page 1223).

[After a clonic seizure] the hindlegs appeared to be in a state of hyperextension, which caused the animal to walk almost on the toes, with the hindquarters well elevated; the forelegs were flexed at the elbows. On walking, stepping was exaggerated in the hindlimbs, with each foot lifted high in turn. In some cases only one hindlimb was involved.

The similarity of these movements to those observed after electrical stimulation of the cerebellar cortex in the unanesthetized cat⁸ was evident. From the cerebellum seizures were obtained which showed three phases: the first, with the stimulus; the second, appearing as a rebound to the first, and immediately after the end of the stimulus, and the third, prolonged and involving the various parts of the animal in a series of relatively slow movements in a definite sequence lasting several minutes. This sequence of movements was further described as resembling a "slow motion" picture.

The present paper is concerned with similar "slow" seizures as produced by stimulation of the cerebral cortex of unanesthetized and unrestrained cats.

METHOD AND MATERIAL

The observations were made on a series of 84 adult cats which, while being used for other experiments, were prepared and stimulated in a similar manner. In 62 of these cats convulsive seizures were produced in the course of the experi-

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ments on them, and so they constitute the significant portion of the series for this study. With the animal under anesthesia induced with soluble pentobarbital U. S. P., electrodes were planted on the cerebral cortex. The cat was stimulated within twenty-four hours, or as soon as the anesthesia had sufficiently abated. The electrode consisted of a stainless steel tube with a tapering threaded end, containing in its axis a silver wire. The wire was fused into the middle of a glass rod, and this was encased in a rubber tube, all of which fitted tightly in the steel tube. The exposed tip of the silver wire embedded in the glass rod was ground flush with the glass, so that it would not injure the brain. The tube was screwed into a trephined hole in the skull far enough to touch the surface of the cerebrum through an opening in the dura. These plugs were allowed to remain for periods ranging from twenty-four hours to two months. From one to six plugs were placed on the cortex of each animal.

Through a detachable extension cord, electrical stimuli of controlled duration and voltage were applied to the cortex. The stimulating current was obtained from the 60 cycle, 110 volt lighting current, passed through a transformer and controlled by a rheostat. The usual duration of stimulation was two to four seconds, and the strength varied from 0.5 to 15 volts, as determined at the time of stimulation by a voltmeter across the leads to the cat.

Conditions of stimulation varied greatly, but usually a threshold response was obtained, requiring from three to five stimuli of low intensity, and then the voltage of a subsequent stimulus was doubled with the purpose of producing a seizure.

Detailed observations were taken on all stimulations, with as careful recording of movements during the seizure as possible.

RESULTS

Of the 62 cats which had convulsions in the course of experiments on them, 30 exhibited the unusual type of seizure to be described. We do not mean to place statistical value on these figures because the series is a select one. The slow seizures were produced by stimulation of many points on the exposed surface of the cerebrum (fig. 1). Other points not indicated in the figure include two on the gyrus cingulus, above the middle of the corpus callosum. The description of the seizure is best made by giving parts of three typical protocols.

CAT 1.—This animal gave a threshold response to a stimulus of 1 volt for two seconds from an electrode on the left motor area. The primary response was extension and protraction of the shoulder and elbow of the right foreleg. Three minutes after the last of seven stimuli at one minute intervals, a stimulus of 9 volts was applied for two seconds.

With the stimulus, there was immediate, strong clonic movement of the contralateral foreleg, followed by strong flexion of the contralateral hindleg. The animal then became quiet, holding a rather strained posture until about forty seconds after the stimulus, when the contralateral forepaw began to lift slowly and rhythmically. The head then turned slowly to the contralateral side and was followed in about ten seconds by replacement of the contralateral foreleg to the floor and slow lifting of the homolateral foreleg until the paw was over the head. For twenty seconds this leg was held thus and then lowered slowly to the floor. Ten seconds later both forelegs were lifted slowly and then gradually replaced,

with slow lifting persisting in the homolateral limb for twenty-five more seconds. The homolateral hindleg then began to lift slowly, the tail being turned in that direction. The cat would respond to stroking. Both hocks were then turned in and subsequently turned outward, with the animal walking in a "cake walk" fashion. Both the hindlegs lifted alternately and slowly, action dying out first in the homolateral leg but persisting in the contralateral one for thirty seconds longer. The tail was turned to the contralateral side while the contralateral hindleg was involved. The entire seizure lasted four minutes, and the cat cried frequently, in a gentle manner.

CAT 2.—This animal had two electrodes on the right frontal cortex; through the anterior one extension of the right forelimb at the elbow and shoulder was elicited with a threshold of 1.5 volts for two seconds. Three previous stimuli were given; then, after a ten minute lapse, a stimulus of 4.5 volts was applied for two seconds. With this stimulus there was strong flexion of the contralateral forelimb, followed by clonus of all four limbs. This persisted for about twelve

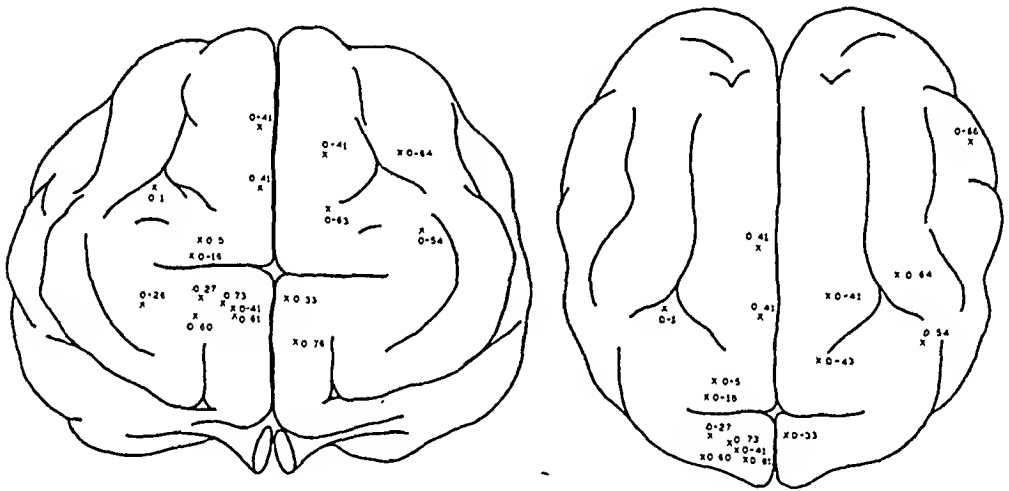


Fig. 1.—Two views of the cerebrum (anterior and dorsal) of the cat, showing the location of points from which slow seizures were elicited by stimulation through implanted electrodes. The cruciate sulcus is conspicuously shown crossing the median longitudinal fissure.

seconds; then the animal got to its feet and slowly lifted the contralateral forepaw. When this extremity was replaced, the contralateral hindleg began to lift slowly and rhythmically. This persisted for about twenty seconds and then ceased; the tail turned to the homolateral side, and after thirty seconds the homolateral hindleg began to lift in a slow manner. After forty seconds all activity ceased. A minute later slow, pleasure reactions appeared in the homolateral forepaw, the head being turned to the homolateral side. The pleasure reactions ceased, and the head turned to the contralateral side for a few seconds and finally returned to the midline. This seizure lasted about five minutes, but the placing reactions were not normal in any of the extremities for over eight minutes. Electrocorticograms were taken during the seizure, but were not conspicuously abnormal.

CAT 3.—This animal was stimulated through an electrode on the anterior end of the posterior suprasylvian gyrus on the right side. With the stimulus (6.7 volts for four seconds) there was immediate extension of the homolateral foreleg.

After thirty-five seconds the contralateral foreleg began to lift slowly, alternating with the homolateral extremity. The contralateral hindleg followed with similar slow lifting. The tail then turned to the homolateral side, followed by turning in and then turning out of the hocks and overstepping of both hindlegs. The homolateral hindleg then lifted slowly, and the cat tended to fall to that side. Twenty-five seconds later the homolateral foreleg lifted high over the homolateral ear. The entire seizure lasted about three minutes.

As seen from the protocols, the typical complete slow seizure occurred on stimulation of the cerebrum with a fairly strong stimulus (as judged by the threshold for elicitation of minimal activity). After such a stimulus, there was usually an immediate strong clonic seizure of short duration which involved strong flexion of the contralateral limbs. There was often associated pupillary dilatation. After a lapse of several

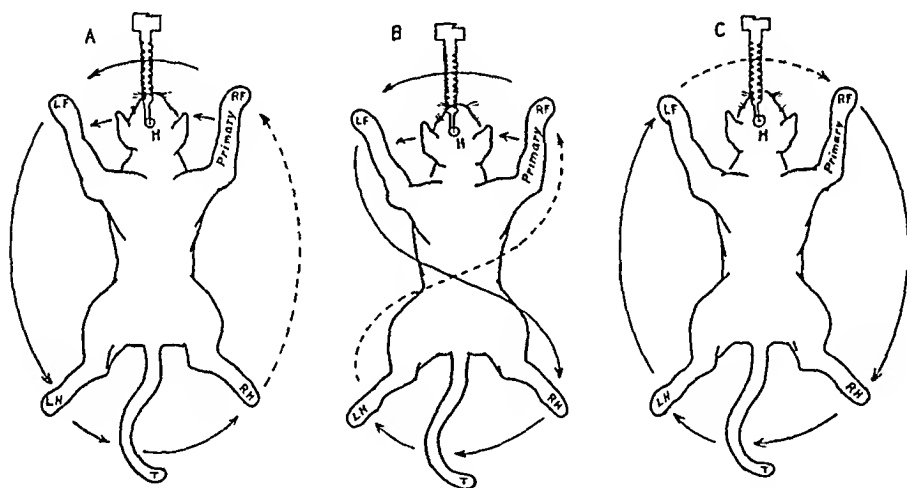


Fig. 2.—Three diagrams designed to show the sequence of involvement of the extremities, head and tail of the cat in the three complete patterns of slow seizures. In each case the stimulus is represented as being applied to the left motor area. The sequence of involvement following response of the primary forelimb is indicated by the solid lines, with arrow points. Dotted lines with arrows indicate the beginning of a possible repetition of the seizures. Similarity in shape of the solid lines with arrows in diagrams *A*, *B* and *C* to the letters *C*, *S* and *U*, respectively, explains the designation of these patterns in the text.

seconds the slow seizure commenced. The opening movement was a slow, deliberate, gentle lifting of the contralateral, "primary" extremity (i. e., a foreleg when the plug was on a "foreleg area"; fig. 3). From this point the sequence was open to some variation. Three general patterns were observed.

The most common sequence of involvement of the limbs we have designated as the *C* pattern (fig. 2 *A*). The contralateral forelimb was usually involved first; then the movement spread to the homolateral fore-

limb. These movements persisted for several seconds, and then the homolateral hindlimb began its slow movements; these in turn were followed by movements of the contralateral hindlimb. The action might then spread back to the primary limb and the entire process be repeated, but this was rare.

The pattern seen next in frequency was the S pattern, which, incidentally, was observed most commonly in the cerebellar seizures⁶ (fig. 2*B*). After the slow lifting of the primary (contralateral) forelimb, the homolateral forelimb was involved in a similar lifting. The next limb to be affected was the contralateral hindleg, followed in sequence by the homolateral hindleg. The action might then start another circuit of the extremities, but, as with the C pattern, it usually died out after the first one was completed.

The third general sequence of involvement of the limbs was termed the U pattern (fig. 2*C*). After involvement of the primary forelimb, the next limb affected was the contralateral hindlimb, which was followed by the homolateral hindlimb and, in turn, by the homolateral forelimb. Again, but rarely, the circuit might be repeated wholly or in part without another stimulus.

The head and tail presented striking patterns of movement during these seizures, but they were not as constant as the movements of the extremities. During a seizure the head tended to turn in the direction of the hindlimb next to be involved. The head and the tail showed a definite tendency, after a turn to one side, to turn to the opposite side. The trunk reacted in a similar manner—strong concavity to one side was followed by strong concavity to the other. The movements of the head, tail and trunk were associated with each of these patterns of the slow seizure.

Throughout these slow seizures the animal appeared to be aware of its surroundings and was responsive to such stimuli as stroking or presenting of food. It seemed not to be especially disturbed by the uncontrolled gyrations of the extremities. An entire seizure varied in length from approximately two to fifteen minutes, but the average duration was about six minutes. After cessation of these movements, there were residual neurologic deficits, such as the loss of the placing reactions, in some animals. Attempts to elicit these were not made in all experiments.

The foregoing description is that of the complete slow seizure, by which is meant a seizure in which all four limbs, the head and the tail are involved. Only about one third of the seizures elicited were complete. Not all seizures exhibited by a single animal on successive trials were complete, but the general pattern of that part of the seizure which appeared remained the same.

Two movement patterns which are characteristic stages of complete seizures have been observed also to occur in and have been used to

identify the incomplete slow seizure. They are: (1) excessive pleasure reactions performed in a slow manner, and (2) high stepping movements of the hindlegs in which the hocks are turned in (fig. 3 *D*) and then turned out in a varus position, so that the animal "cake walks."

The pleasure reaction is the typical response of the animal to petting under normal circumstances and is the normal kitten's reaction while nursing. It is a dainty lifting of the paws, together with flexion of the toes and protrusion of the claws of the forefeet. It is executed rhythmically and alternately by the forelegs. In the slow seizure, it is first seen in the contralateral (primary) foreleg and then in the homolateral extremity, so that the two are involved simultaneously awhile, but the reaction tends to die out in the primary leg first. (In the complete type of slow seizure this response progressively changes to the high lifting movements.) During this type of response the animal frequently

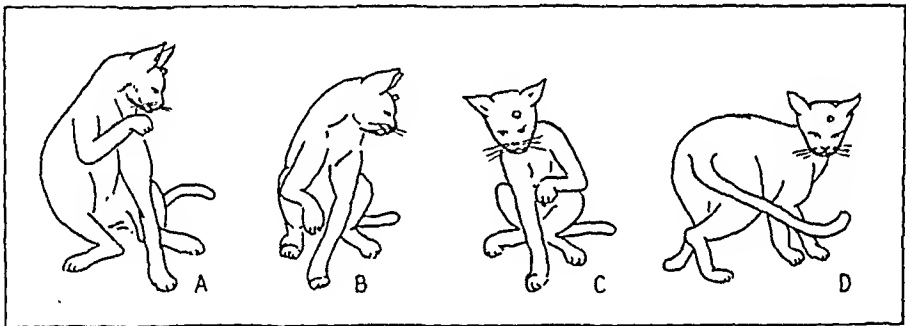


Fig. 3.—Sketches traced from portions of a moving picture of a cat taken during a slow seizure. The poses from *A* through *D* represent successive stages in the sequence of a seizure, such as that elicited from the left motor area.

purrs. The hock movements in the hindlimbs were seen in association with the pleasure reactions and were usually of longer duration.

It is difficult to define at just what point a slow seizure began and where it ended; however, in our observation, the occurrence of the pleasure reaction and the hock movements were considered to constitute the shortest possible slow seizure.

Certain operative procedures were carried out on some of these animals. In 2 cats bilateral ablation of the motor areas failed to affect either the slow seizure or the pattern thereof. In experiments designed to limit the spread of the neuronal discharge through cortical fibers by cutting through the cortex cerebri around the stimulated area, no alteration in the fit or the pattern was observed in 3 animals. In none of these was the cutting complete enough to isolate the point from the neighboring cortex. The slow seizure was not reproduced in 2 animals after removal of the cerebellum (though it had appeared from stimuli applied to the same electrode before removal of the structure), but it was

possible to produce a jacksonian type of seizure from the same point after its removal.

Section of one basis pedunculi in 1 animal was followed by a striking alteration in the sequence of limb movements, but made no difference in the type of movement. Prior to section of the basis pedunculi this animal showed a typical S pattern (fig. 2*B*). After the section, the response of the contralateral, primary limb was at first absent, the sequence continuing as before, with the primary limb involved last.

Section of the corpus callosum of 1 animal likewise did not abolish the type of seizure, but it was followed by alteration of the sequence of the limb movements. Prior to section of the corpus callosum, the pattern was of the C type; however, during a seizure after sectioning, slow movements of the contralateral foreleg did not appear, while the head and tail (midline structures) were involved to a much greater degree. The hindlegs were involved simultaneously after the head and tail had completed their movements.

COMMENT

Seizures of such similar character elicited from stimulation of the cerebrum or cerebellum suggest intimate relationships and bring to mind the occasional difficulty in distinguishing clinically between lesions of the frontal lobe of the cerebrum and those of the cerebellum. In the case of lesions of the two areas destruction of tissue and perhaps functional deficits are most conspicuous, in contrast to the present experiments, in which excitation of the two regions is involved primarily. It is of course possible that the effects observed here are also related to functional deficits, since the negative placing reactions may imply temporary abeyance of cortical function.

In the observation of the slow seizure, as elicited from the cerebral cortex of the cat, it has not been possible, to date, to determine the mechanism of spread and production or the exact localization. However, certain generalizations and inferences can be drawn.

The similarity of the slow seizures elicited from the cerebrum to those obtained from mechanical or electrical stimulation of the cerebellar cortex is so striking that for convenience we have come to term those elicited from regions other than the cerebellum "cerebelloid" seizures. While the origin of the seizures is obscure, some points suggest a definite cerebellar involvement: (1) the nature of the movements—slow, deliberate, graceful and identical in character with those produced after stimulation or production of small lesions of the cerebellar cortex; (2) the "rebound" phase of almost every movement—i. e., a movement of a limb is paired with a similar movement of the opposite one, and movements of the head, body and tail alternate in direction; (3) the extreme lability of the seizure to fatigue, drugs, etc., which is also true

of cerebellar seizures, and (4) the failure to reproduce the cerebelloid seizure in 2 animals (electrodes on the cerebral cortex) after removal of the cerebellum, although the rapid clonic seizure was elicited. In the light of the third point the fourth has less significance than might be indicated.

It appears likely that the cerebelloid seizures occur with much greater frequency than is suggested by the 30:62 ratio and that they are overshadowed by the less labile clonic convulsions. At times the clonic fits last for as long as several minutes after strong stimuli, and alterations in the posture (flexion or extension) of the clonically involved limbs are frequently slow and may represent the cerebelloid pattern with clonus superimposed. A careful analysis of slow motion moving pictures of cats during the clonic attacks would be important in demonstrating the presence or absence of a cerebelloid sequence. This possible interpretation is further supported by the fact that the end of a cerebelloid sequence is often the only obvious evidence of the cerebelloid attack after the clonic movements have ceased.

That visceral activity (except pupillary dilatation, which also accompanies true cerebellar seizures) apparently is absent in the cerebelloid attacks, although it is an important component of the clonic seizure, suggests that two projection systems are involved, either from the cortex (the point stimulated) or from some lower "level." Obviously, autonomic pathways are involved in the clonic attacks, and it appears likely that these are not completely of cortical origin, since large cortical ablations do not prevent their occurrence. It would be valuable to know whether the pupillary dilatation is the result of the activity of the dilator muscles or of the constrictor muscles (oculomotor inhibitions) of the iris, in view of Hodes and Magoun's⁹ demonstration of the widespread origin of the latter and the relatively limited regions of origin of the former.

Certain predisposing factors may be involved in production of the cerebelloid seizure. It has been noted repeatedly that such a seizure was more frequently elicited from an animal of gentle disposition, and if the cat was angered or irritated, the seizures were often not elicited (inhibited or submerged). The similarity of certain phases of the cerebelloid seizure to normal actions and motions (though caricatured) of the cat is also striking, such as the pleasure reactions, the slow movements of the body and tail and, not infrequently, the associated purring.

The location of the stimulating electrode on the cortex may be a factor in the elicitation of the cerebelloid seizure; seizures have occurred, however, after stimulation of surface points both in and out of the "motor" area and on the gyrus cinguli, on the median surface of the brain. That cerebelloid seizures could be elicited after removal of the motor areas

9. Hodes, R., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Forebrain and Midbrain with Special Reference to the Pupil, *J. Comp. Neurol.* **76**:169-190, 1942.

or after section of one basis pedunculi indicates that integrity of the pyramidal tract is not essential for the slow type of seizure, a conclusion which also holds for the clonic fits (unpublished experiments; Ward and Clark ⁶).

SUMMARY AND CONCLUSION

An unusual type of seizure following electrical stimulation of the cerebral cortex of the unanesthetized cat is described. The seizure is slow and strikingly similar to that elicited from the cerebellar cortex of the unanesthetized cat. Its mechanism is yet to be determined. It is a distinct entity, quite separate from the usual "jacksonian seizure" also elicited from the cerebral cortex.

Vanderbilt University College of Medicine.

PARAPHENYLENEDIAMINE POISONING WITH CHANGES IN THE CENTRAL NERVOUS SYSTEM

CHARLES DAVISON, M.D.

NEW YORK

The prevalent use by women of coal tar products as hair dyes, sold in the market under various trade names, is well known. "Ursol," a paraphenylenediamine coal tar chemical, is a popular preparation. When such a dye is used excessively, vertigo, gastritis, diplopia, asthenia and exfoliative dermatitis may result. Although neurologic complications, such as dizziness, nystagmus and tinnitus, have been recorded, histopathologic reports of involvement of the central nervous system were not found in the literature.

REPORT OF A CASE

L. M., a woman aged 51, was admitted to the Montefiore Hospital on Dec. 22, 1939 with a history that for about one and a half years she had been dyeing her hair with "ursol." In December 1938 she experienced pain in the knees. In June 1939 she noticed yellowish discoloration of the entire skin and the finger nails. In August 1939 she complained of dyspnea on exertion, occasional palpitation and loss of about 30 pounds (13.6 Kg.) in weight. During this interval there was low grade fever. In the early part of September 1939 there appeared tender blisters over the tongue, which slowly subsided. At this time the patient suffered from abdominal pain, pronounced anorexia and weakness.

General Examination.—There was a peculiar, yellow-grayish discoloration of the skin of the entire body and of the nails which matched the color of the dyed hair. The dorsum of the tongue was smooth. The heart was slightly enlarged to the left, and the second aortic sound was greater than the second pulmonic sound. There was some evidence of auricular fibrillation. The blood pressure was 110 systolic and 70 diastolic. The liver was 4 fingerbreadths and the spleen 3 fingerbreadths below the costal margin. Motion of the interpharyngeal joints was decreased.

Neurologic Examination.—There were deep muscle tenderness of both calves; slightly exaggerated reflexes, especially in the lower extremities; left ankle clonus; absence of abdominal reflexes, and a questionable Babinski sign bilaterally. No evidence of sensory changes was apparent. There was suggestive facial paralysis of supranuclear type.

From the Neuropathologic Laboratory and Neuropsychiatric Service of the Montefiore Hospital for Chronic Diseases.

This paper was read at a joint meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, and the New York Neurological Society on March 10, 1942. The discussion appeared in the October 1942 issue of the ARCHIVES, page 672.

Laboratory Data.—The urine contained albumin, 2 white cells per cubic millimeter and granular and hyaline casts. Examination of the blood disclosed 72 per cent hemoglobin, 3,600,000 red cells and 5,750 white cells, with 38 per cent polymorphonuclear leukocytes, 16 per cent metamyelocytes, 2 per cent myeloblasts, 27 per cent lymphocytes, 4 per cent mononuclears, 2 per cent eosinophils and 1 per cent basophils. The blood smear showed anisocytosis, macrocytosis, poikilocytosis and polychromatophilia.

Roentgen examination of the skeletal system revealed hypertrophic changes in the spine, hip joints, sacroiliac bones and bones of the lower extremities and hands.

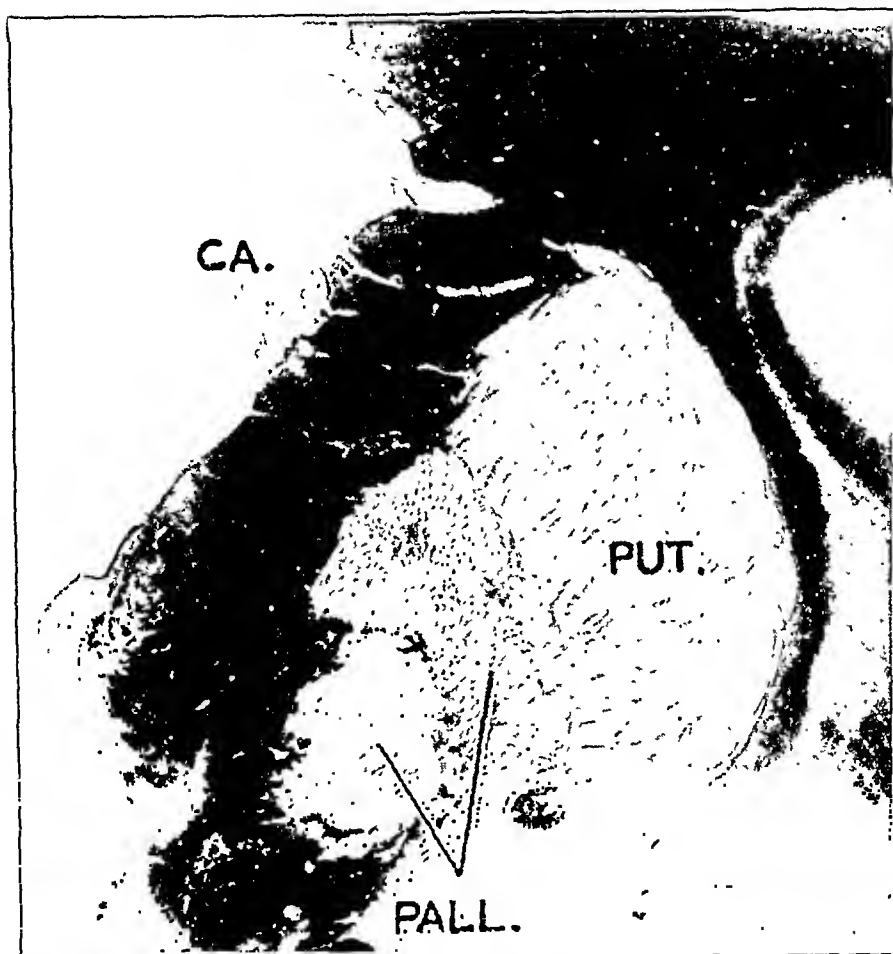


Fig. 1.—Pallor of the pallidal segment, thinning of the ansa lenticularis and slight status marmoratus of the putamen. Myelin sheath stain.

Course.—During her stay in the hospital the patient complained repeatedly of severe asthenia, anorexia and epigastric pain and appeared drowsy. She had a low grade fever, the temperature ranging from 99 to 100 F. and rising nightly to 102 F. She received all forms of vitamin therapy, which led to disappearance of the glossitis. The neurologic picture remained unchanged. The aforementioned symptoms became more severe, and for about two months before death the knee and ankle jerks were unobtainable and there were definite left ankle clonus and Babinski sign bilaterally. The anemia became more severe. She received several transfusions, but her condition gradually became worse, and she died on March 9, 1940.

General Pathologic Observations.—The skin was yellowish gray. Hepatosplenomegaly, ascites and atherosclerosis of the coronary arteries and aorta were observed on gross inspection. The liver was 4 fingerbreadths below the costal margin and weighed 2,500 Gm. The capsule had a glistening appearance, and the underlying tissue was moderately granular. The organ cut with increased resistance. Microscopically, there were atrophy of the hepatic cords, foci of necrosis of liver cells and occasional areas of proliferation of biliary ducts. The

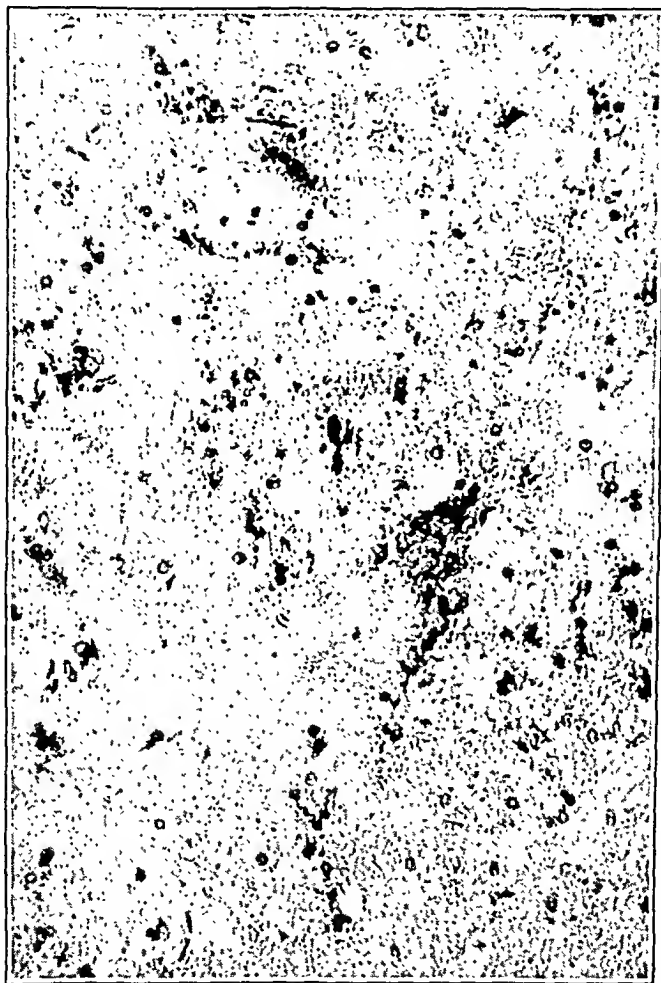


Fig. 2.—Pigmentary accumulations in pallidal segments. Turnbull blue stain; $\times 200$.

spleen was tremendously enlarged, weighed 1,420 Gm. and was firm. There was an infarction in the upper pole. Microscopically, the follicles appeared indistinct, and the pulp was greatly congested. The area of infarction at the edge was fairly well demarcated from the adjacent splenic tissue by an extremely congested zone.

Brain and Spinal Cord.—Gross Examination: The dura, especially the under surface, had a yellowish tinge. The brain had a pronounced pallor and weighed

1,420 Gm. The pia-arachnoid stripped readily. No other abnormalities were noted. Except for pallor, the cord showed no abnormalities.

Microscopic Examination: Sections from various regions of the cortex, diencephalon, dentate nucleus, cerebellum, brain stem and spinal cord were stained for

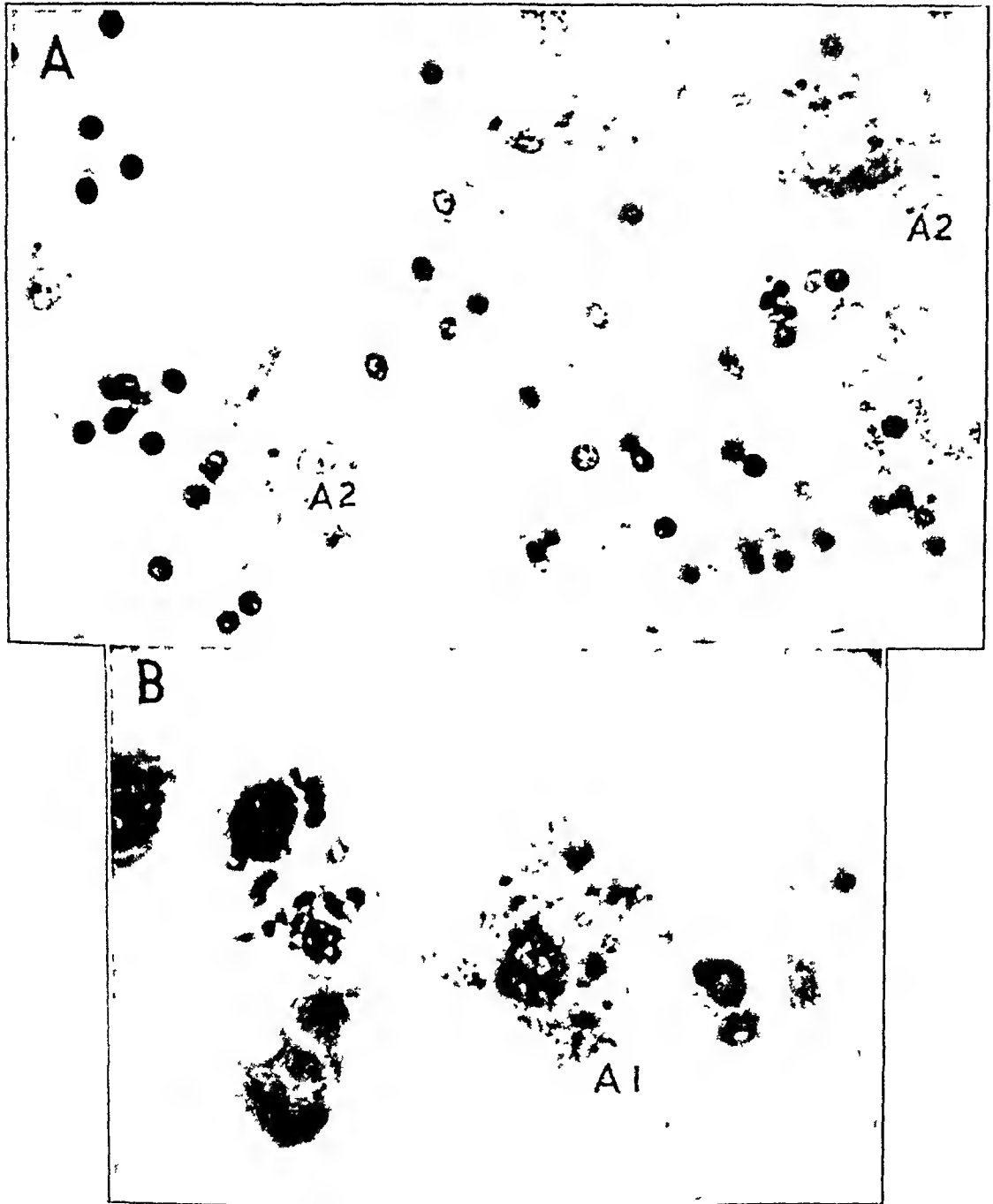


Fig. 3.—*A* ($\times 400$), Alzheimer cells type II, with slight accumulation of pigment granules around them. Notice the diseased pallidal nerve cells. *B* ($\times 900$), Alzheimer cells type I. Cresyl violet stain.

myelin sheaths and with cresyl violet. Some of the sections of the cortex and the basal ganglia were fixed in alcohol and stained with cresyl violet and with Turnbull blue. Frozen sections were also stained by the myelin sheath, Bielschowsky, sudan III and Holzer methods.

Cortex: Sections from various regions of the cortex disclosed a normal arrangement of the cytoarchitectural layers, with preservation of the nerve cells. An occasional nerve cell showed evidence of chromatolysis. There were also a few Alzheimer glia cells type II, surrounded by a slight amount of pigment.

In the hippocampus, in addition to the aforementioned changes, there were numerous accumulations of amyloid bodies. The slight changes in the ganglion

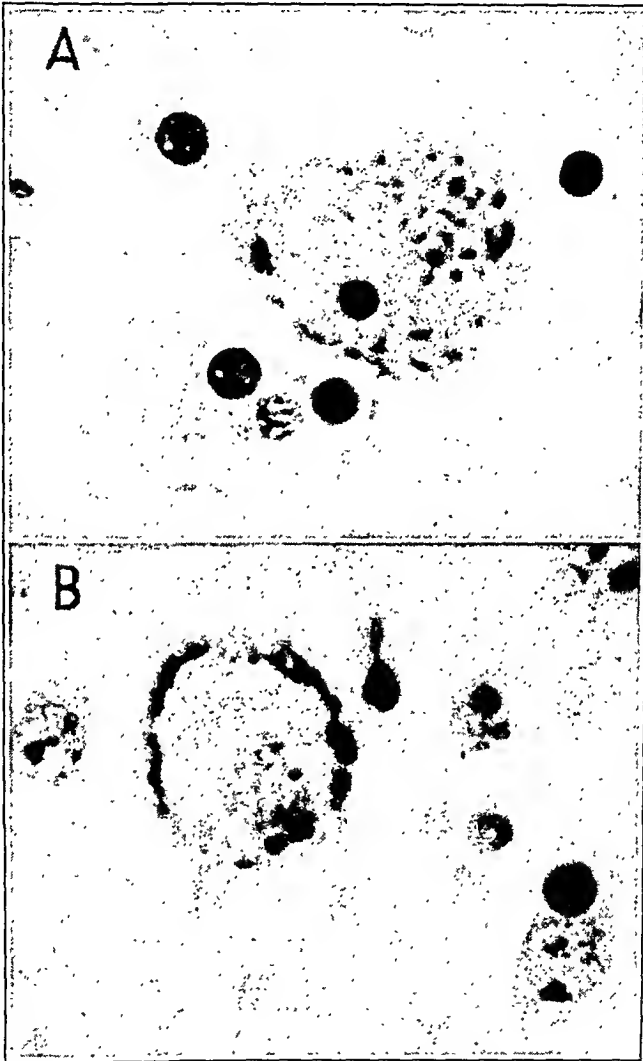


Fig. 4.—*A* ($\times 1,200$), pigment accumulations in one of the nerve cells, with the nucleus displaced to the periphery. *B* ($\times 900$), chromatolysis, accumulation of Nissl substance at the periphery and collections of pigment granules. Cresyl violet stain.

cells were more prominent in this than in the other cortical regions. Sommer's sector appeared normal.

Diencephalon: Sections were made of the basal ganglia through the rostral part of the pallidum. There was pronounced pallor of both pallidal segments (fig. 1), with almost complete disappearance of the ansa lenticularis. The putamen had a slight

marble-like appearance (fig. 1). With high power magnification the myelin sheaths of the pallidal fibers showed slight swelling and beading. An occasional swollen axis-cylinder was noted. In the Turnbull blue preparations the entire pallidum took a bluish stain. There were heavy deposits of bluish iron pigment throughout the pallidal segments (fig. 2), with numerous Alzheimer cells types

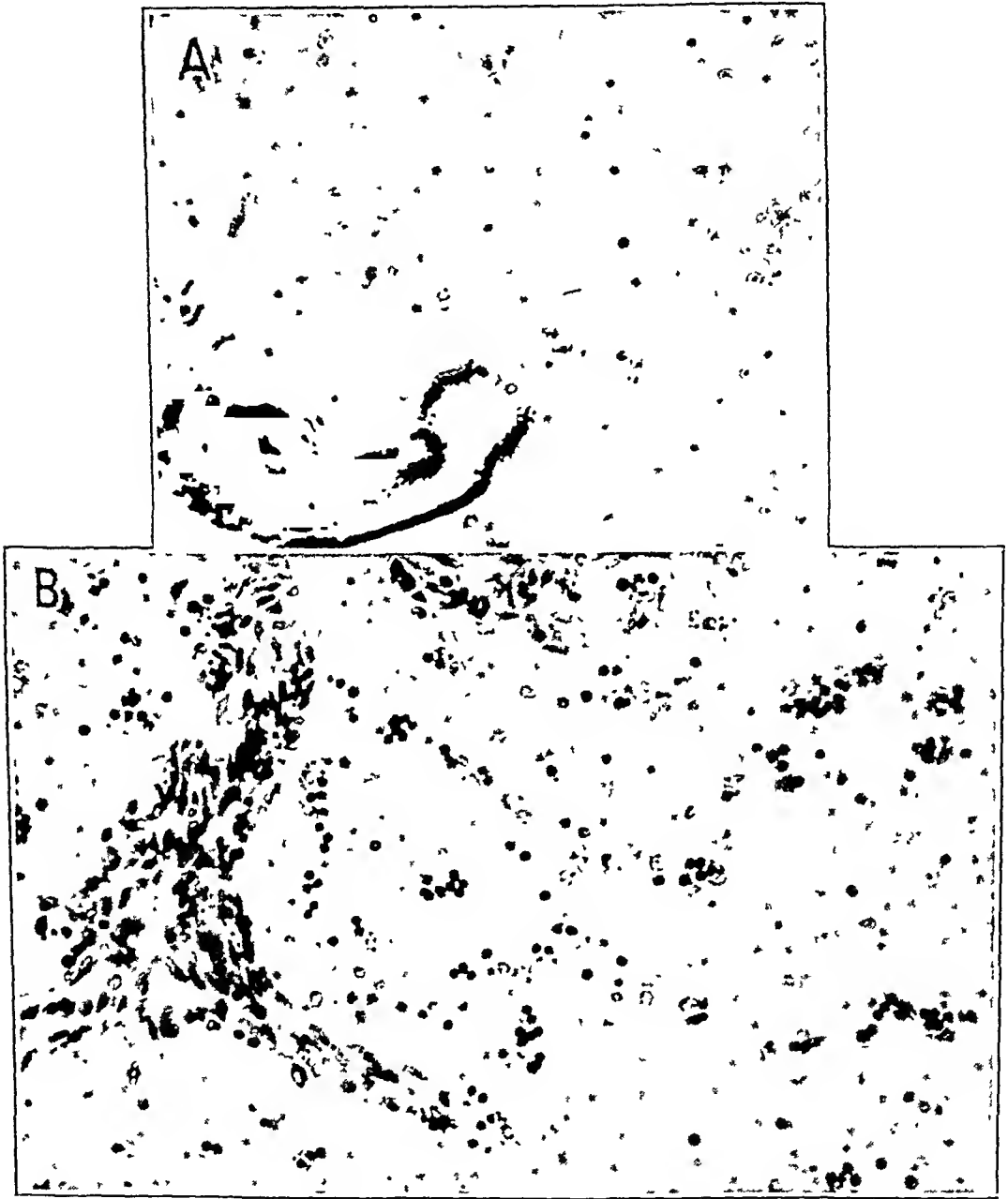


Fig. 5.—*A* ($\times 190$), calcific and iron deposits around a vessel. Notice the pigmentary deposits in the pallidal nerve cell. *B* ($\times 190$), proliferating vessels of the basal ganglia and increase in the glia nuclei. Cresyl violet stain.

I and II (fig. 3 *A* and *B*). Heavy deposits of bluish pigment were also observed in the walls of the vessels. The entire striatum took a pinkish stain, in contrast to the bluish stain of the pallidum. It contained fewer Alzheimer cells and less iron deposits than the pallidum. In the cresyl violet preparations the pallidal nerve cells were decreased in number; they appeared pale and showed marked

loss of chromatin material or were almost completely disintegrated (fig. 3 *A* and *B*). Many of the pallidal nerve cells contained heavy brown-bluish pigmentary deposits, which were usually situated at the periphery of the cell (fig. 4 *A*). In other cells the Nissl substance had collected at the periphery, and the pigment granules were usually situated at one of the poles of the cell (fig. 4 *B*). The pigmentary deposits were somewhat similar to the accumulations seen in cases of pigment atrophy. They differed somewhat from the latter in that they consisted

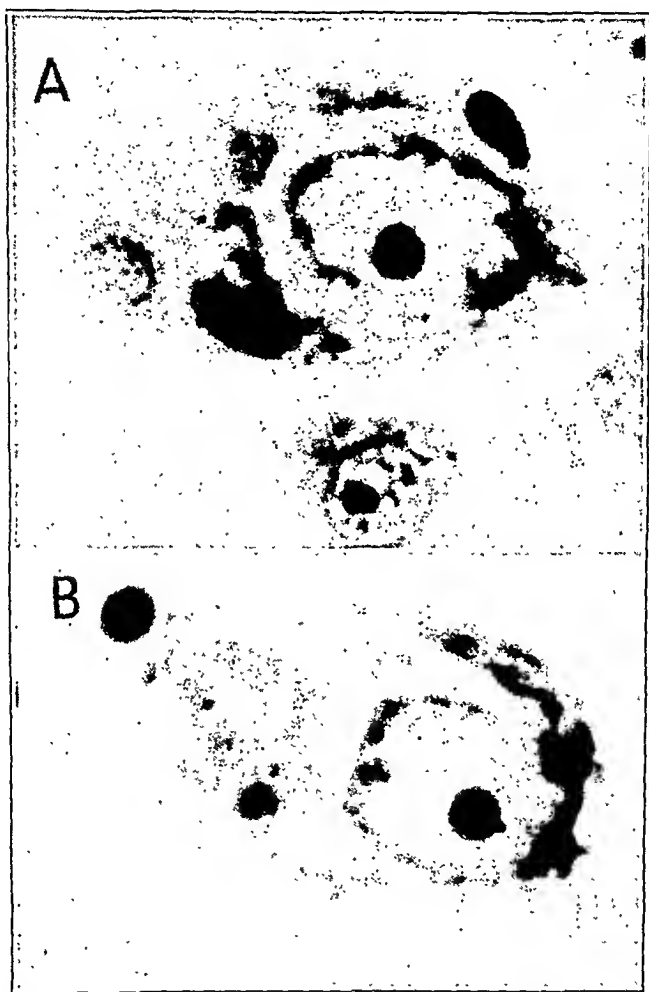


Fig. 6.—*A* ($\times 1,200$), diseased nerve cell of the striatum, with some pigment accumulation and tendency of Nissl substance to accumulate at the periphery. *B* ($\times 1,200$), severe disintegration of the nerve cell of the striatum. Cresyl violet stain.

of heavy granules (fig. 4 *A* and *B*). A number of the pallidal nerve cells were completely destroyed. They were recognized only by their nuclei and nucleoli, which, in turn, were surrounded by deposits of pigment (figs. 3 *A* and *B*). Some of the pallidal vessels were calcified (fig. 5 *A*), and others disclosed proliferation of the endothelial cells (fig. 5 *B*). In the striatum, the large nerve cells revealed changes somewhat similar to those of the pallidum, but less extensive. Some

showed chromatolysis, with a tendency for the Nissl granules to accumulate at the periphery of the nerve cell (fig. 6*A*), while others were severely diseased (fig. 6*B*). Sections through the middle of the striatum and pallidum disclosed changes similar to but far less extensive than those in the rostral portion of the pallidum. The nerve cells of the thalamic nuclei stained normally. There were no pigmentary deposits or Alzheimer cells.



Fig. 7.—Nerve cells of the dentate nuclei with pigmentary deposits. Cresyl violet stain; $\times 400$.

Hypothalamus: The lining of the third ventricle was slightly thickened. There were numerous deposits of amyloid bodies. The nerve cells of the hypothalamus showed some loss of their heavy iron pigment granules. In addition, many of the nerve cells, especially in the supraoptic nucleus, contained the same type of pigmentary deposit as did the nerve cells of the pallidum.

Cerebellum and brain stem: In the myelin sheath preparation the dentate nucleus showed no abnormalities. In the cresyl violet preparation there were

pigment atrophy of many of the nerve cells, ischemic cell changes, occasional chromatolysis and a few Alzheimer cells, surrounded by pigmentary deposits. Some of the nerve cells of the dentate nucleus showed the same heavy granular deposits as did the pallidal nerve cells (fig. 7). The nerve cells of the inferior olivary nuclei, except for pigment atrophy of the typical variety, were normal. The Purkinje cells appeared intact.

Spinal cord: No areas of demyelination were noted, but there were numerous amyloid bodies and the central canal was patent. A few of the anterior horn cells did not stain well, but did not present pathologic changes.

COMMENT

Most of the hair-dyeing agents are derivatives of phenylenediamine. There are several varieties: the ortho, meta and para and the dimethyl and diethyl derivatives. The paraphenylenediamine used by this patient is a dark or black crystalline, solid material with a melting point of 140 C. and a boiling point of 267 C. The dark color is due to the combination of the dye with iron. The compound is unstable, and on exposure it oxidizes and turns black, especially in an aqueous solution. It is difficult to purify. It crystallizes in benzine and is easily soluble in alcohol and ether. It can be oxidized by the blood and all the tissues of higher animals, especially the brain, heart, muscles, kidneys and liver. The reaction is facilitated by the presence of water.

The substance is used commercially under the name of "ursol" for dyeing furs and in hair dyes. Many cases of paraphenylenediamine poisoning have been reported. The symptoms elicited are vertigo, gastritis, diplopia, asthenia and dermatitis, especially of the exfoliative type. The acute onset is also characterized by dizziness, nystagmus and tinnitus. When the dye is used over a prolonged period gradual deafness may take place. Improvement occurs when the dye is removed. Some symptoms have been reported from the dye used in cosmetics and stockings. Asthma and eczema have been observed in workers using this dye in vulcanizing rubber industries, in fur-dyeing and feather-dyeing industries, in photographic developing and in textile dye intermediaries.

Experimentally, the dye produces in the rabbit edema of the head and neck. In addition, in rabbits and cats a rapid pulse and increased respiration, with wheezing and hypothermia, develop. Convulsive seizures have been reported to occur in some mammals. Asthma is due perhaps to the constricting action of the dye on the bronchiolar musculature. It acts like histamine in stimulating smooth muscle and increasing capillary permeability, and thus produces edema. The meta derivative, when used experimentally, causes hydrothorax, chemosis, exophthalmos and lacrimation.

As already stated, numerous cases have been reported clinically (Close,¹ Möllerström² and Nott³), and in some instances references have been made to neurologic signs and symptoms, but no cases with pathologic studies of the central nervous system have been described. In the cases in which necropsy was performed (Israëls and Susman⁴ and Peters and Sachs⁵) the lesions observed were acute, subacute or focal necrosis of the liver, hepatosplenomegaly, severe congestion of the viscera and anemia. Israëls and Susman⁴ mentioned that "the brain showed a definite acute congestion of the cortex and white matter throughout. The appearance was that of a toxic encephalitis." Apparently, microscopic examination had not been made. Peters and Sachs⁵ reported clinically a case of impairment of proprioceptive sensation and apparent loss of vibratory sensation below the third lumbar vertebra. Unfortunately, the central nervous system in this instance was not obtained at autopsy. Neurologic complications were also mentioned by Close¹ and Keschner and Rosen.⁶ In Close's¹ case nystagmus, tinnitus, giddiness and headaches were the outstanding neurologic symptoms. Keschner and Rosen⁶ described a case in which the sole observation was papilledema and retinal hemorrhages. At first the possibility of an expanding intracranial lesion as the etiologic factor was considered, but careful investigation revealed that the patient was using a hair dye sold under the name of "Glo-Rniz." The following note appeared on the label of this product, as required by the federal Food, Drug and Cosmetic Act for all "coal tar hair dyes."⁷

1. Close, W. J.: A Case of Poisoning from Hair Dye (Paraphenylenediamine), *M. J. Australia* **1**:53 (Jan. 9) 1932.

2. Möllerström, J.: Acute Intoxication from the Use of Aniline Dyes, *Acta med. Scandinav.* **71**:73, 1929.

3. Nott, H. W.: Systemic Poisoning by Hair Dye, *Brit. M. J.* **1**:421 (March 8) 1924.

4. Israëls, M. C. G., and Susman, W.: Systemic Poisoning by Phenylene-diamine: Fatal Cases with Pathological Report, *Lancet* **1**:508 (March 10) 1934.

5. Peters, H. R., and Sachs, M. S.: Systemic Poisoning Due to Synthetic Organic Hair Dye: Fatal Case with Autopsy, *Ann. Int. Med.* **12**:2032 (June) 1939.

6. Keschner, M., and Rosen, V. H.: Optic Neuritis Caused by a Coal Tar Hair Dye, *Arch. Ophth.* **25**:1020 (June) 1941.

7. Federal Food, Drug and Cosmetic Act and General Regulations for Its Enforcement, Service and Regulatory Announcements, Food, Drug and Cosmetic, no. 1, Food and Drug Administration, United States Department of Agriculture, 1939, sect. 601 A.

This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to the accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Ocular disturbances are most likely the result of application of these dyes to the eyelashes and eyebrows. Toxic optic neuritis, as in Keschner and Rosen's⁸ case, is an unusual complication of this type of poisoning. Berger⁸ and Veasey⁹ also reported cases of toxic optic neuritis in patients who used aniline dyes.

In the case reported by Keschner and Rosen,⁸ a strong solution of ammonia was used to remove the dye from the forehead, and this may have been a factor in the toxic optic neuritis. Mackenna¹⁰ and Israëls and Susman⁴ expressed the belief that it is dangerous to attempt to remove the dye from hair with hydrogen peroxide or sodium thiosulfate, as use of these substances may intensify the symptoms. Baldrige¹¹ emphasized that application of heat and ammonia during the giving of a "permanent wave" may aid in the rapid absorption of the dye.

The outstanding neurologic signs in the case presented were asthenia, anorexia, drowsiness, muscle tenderness, slightly exaggerated deep reflexes, left ankle clonus, absence of abdominal reflexes and plantar responses.

The essential histopathologic changes in the central nervous system were observed in the pallidum, the striatum, the hypothalamus and, to a slight extent, in the dentate nucleus. These consisted essentially of peculiar granular deposits in the nerve cells, which were similar to those seen in the oxidase reaction. The other pathologic changes in the nerve cells, the deposits of iron pigment and the Alzheimer cells in the striatum and pallidum were similar to those observed in cases of severe disease of the liver. The pathologic picture in this case consisted, therefore, of primary and secondary changes as a result of the paraphenylenediamine poisoning. The chemical which circulated in the blood stream in this instance induced the oxidase reaction in the nerve cells and other tissues of the body. The heavy pigment granules and the proliferation of the smaller pallidal vessels, similar to what is seen in cases of lead poisoning, were undoubtedly due to the direct action of the toxin on the nerve cells and the blood vessels. The primary process in the liver caused the secondary changes in the central nervous system. The iron deposits, the Alzheimer cells and the chromatolytic changes in the nerve cells of the striatum and pallidum were most likely secondary to the involvement of the liver.

8. Berger, A.: Visual Disturbances Due to the Use of Hair Dye Containing Aniline, *Arch. Ophth.* **38**:397, 1909.

9. Veasey, cited by Berger.⁸

10. Mackenna, R. M. B.: Modern Cosmetic Preparations: Their Chemical Composition, and Pathological Developments Attributable to Them, *Brit. M. J.* **1**:899 (May 17) 1930.

11. Baldrige, C. W.: Macrocytic Anemia with Aplastic Features Following Application of Synthetic Organic Hair Dye, *Am. J. M. Sc.* **189**:759 (June) 1935.

CONCLUSION

A case of paraphenylenediamine poisoning following the use of a popular hair dye named "ursol" is reported. In addition to the typical clinical and pathologic changes following such an intoxication, neurologic signs and symptoms, with pathologic changes in the central nervous system, also developed. The most important of these changes was the oxidase reaction, resulting in deposits of pigment granules in the nerve cells of the pallidum, the striatum, the hypothalamus and the dentate nucleus.

TREATMENT OF SCHIZOPHRENIA

FOLLOW-UP RESULTS IN CASES OF INSULIN SHOCK THERAPY AND IN CONTROL CASES

JACQUES S. GOTTLIEB, M.D.

AND

PAUL E. HUSTON, M.D., PH.D.

IOWA CITY

The purpose of this report is to compare the results of insulin shock therapy in a group of schizophrenic patients with the results of conservative treatment in a group of similar patients used as controls. The control group has been reported on previously.¹ The criteria for diagnosis and such factors as economic, occupational and educational levels and racial composition were the same in the two groups. Likewise, the selection of the patients for admission to the hospital was identical. Thus the groups were directly comparable, and the value of insulin shock therapy can therefore be estimated.

METHOD

Sixty-six patients suffering from schizophrenia, in whom the disease processes were typical, were treated by means of insulin shock. This procedure was made routine; it consisted, briefly, of giving the patient progressively larger amounts of insulin until the dose was sufficient to produce coma within two or three hours after injection. The patient was allowed to remain in coma from one-half to three hours. The depth of coma was determined by the absence of the corneal reflex. Each patient was subjected to thirty periods of coma at the rate of six per week. It was found that with successive treatments progressively smaller amounts of insulin were required to produce the same desired depth of coma. Therefore our criteria for treatment were depth and number of comas. After the series of treatments the patient was kept in the hospital from three to four weeks before discharge.

After the patient left the hospital his condition was evaluated clinically at six month intervals, the minimum final follow-up period being one year and the maximum four years. The clinical status of the patient was rated according to four categories: 1. Complete recovery. The patient had lost all psychotic symptoms and was able to adjust on or above his previous social level. 2. Social recovery. The patient continued to show minor defects which were not noted by his associates and was adjusting socially at approximately his former level. 3. Improve-

From the Iowa State Psychopathic Hospital, State University of Iowa College of Medicine.

1. Malamud, W., and Render, N.: Course and Prognosis in Schizophrenia, *Am. J. Psychiat.* 95:1039-1055 (March) 1939.

ment. The patient continued to show defects but was able to live in the community, adjusting, however, at a lower level than previously. 4. No improvement. The patient continued to show psychotic manifestations of the same degree as when he was in the hospital or had deteriorated. A fifth classification included patients who had died.

MATERIAL

These 66 patients were free from other diseases, as determined by their physical and neurologic status and by ordinary laboratory procedures. Thirty-six were men, and 30 were women. The ages ranged from 14 to 44 years, the average being 25.1 years. The average length of stay in the hospital, including the period of treatment, was twelve weeks. The schizophrenic subtypes were represented as follows: simple, 4 patients; catatonic, 3 patients; hebephrenic, 21 patients; paranoid, 14 patients, and unclassified, 24 patients.

The control group contained 132 patients: 60 men and 72 women. The average age was 28.4 years; the age range, from 13 to 58 years. The average length of hospitalization was seven weeks. The representation of the subtypes was as follows: simple, 12 patients; catatonic, 6 patients; hebephrenic, 39 patients;

TABLE 1.—*Comparison of the Final Clinical Status of Schizophrenic Patients Treated with Insulin Shock and That of a Control Group Over the Same Follow-Up Period of One to Four Years*

Group	Number	Complete Recovery	Social Recovery	Complete and Social Recovery	Improvement	No Improvement	Improvement and No Improvement	Dead
Insulin-treated.....	66 (100%)	8 (12%)	15 (23%)	23 (35%)	8 (12%)	34 (52%)	42 (64%)	1 (1%)
Control.....	132 (100%)	28 (21%)	15 (11%)	43 (33%)	14 (11%)	71 (54%)	85 (64%)	4 (3%)

paranoid, 24 patients, and unclassified, 51 patients. The original data of Malamud and Render¹ were reexamined to obtain a control group having a comparable follow-up period.

The insulin-treated and the control group were drawn from the same racial, economic and cultural population, as nearly all were natives of Iowa. The selection of patients for admission to the hospital was also the same for the two groups. In general, chronic deteriorated patients were not admitted. In this way our groups differed from the usual state hospital population. The diagnostic criteria were also uniform. It may be noted from the foregoing figures that the control group was twice as large as the insulin group, but the relative percentages of the schizophrenic subtypes in the two groups were about the same. The period of stay in the hospital of the insulin group averaged five weeks longer than that of the control group. This was due to the additional time consumed by the insulin treatment.

RESULTS

In table 1 is compared the final clinical status of the two groups of schizophrenic patients. The subsequent courses for these groups were over the same interval of one to four years. From this table it would appear that there are differences between the two groups in the categories of complete and social recovery, the control group being favored

in the category of complete recovery and the insulin-treated group in the category of social recovery. Since, however, it was difficult to estimate whether a patient was completely or socially recovered, these differences are probably not significant. A more meaningful comparison may be obtained by combining the categories of complete and social recovery and those of improvement and no improvement. The percentages for the first combination are 35 for the insulin-treated group and 33 for the control group. For the second combination the percentages are 64 for each group. It is evident, therefore, that insulin did not increase the rate of remission of the insulin-treated patients as compared with that for the group treated conservatively.

TABLE 2.—*Clinical Status at Various Follow-Up Periods of Patients Treated with Insulin*

Group	Time After Discharge	Number	Complete Recovery	Social Recovery	Complete and Social Recovery	Improvement	No Improvement	Improvement and No Improvement
Insulin.....	Discharge	66 (100%)	1 (1%)	12 (18%)	13 (19%)	19 (29%)	34 (52%)	53 (81%)
	6 mo.	66 (100%)	8 (12%)	12 (18%)	20 (30%)	17 (26%)	29 (44%)	46 (70%)
	1 yr.	65 (100%)	8 (12%)	11 (17%)	19 (29%)	14 (22%)	32 (49%)	46 (71%)
	2 yr.	45 (100%)	5 (11%)	10 (22%)	15 (33%)	5 (11%)	25 (56%)	30 (67%)
	3 yr.	16 (100%)	3 (19%)	4 (25%)	7 (44%)	1 (5%)	8 (50%)	9 (56%)
	4 yr.	9 (100%)	1 (11%)	1 (11%)	2 (22%)	2 (22%)	5 (56%)	7 (78%)
Control *.....	16-28 mo.	39 (100%)	12 (31%)	2 (5%)	14 (36%)	5 (13%)	20 (51%)	25 (64%)

* The figures for the control group for a follow-up period of sixteen to twenty-eight months are included for comparison.

In table 2 is presented the clinical status by categories of the insulin-treated patients at the time of discharge and at intervals of six months, one year, two years, three years and four years thereafter. The figures for the control group for the sixteen to twenty-eight month follow-up periods are included for comparison. From this table it seems clear that for the periods of six months, one year and two years the figures for the combined categories of complete and social recovery for the insulin group are similar to those for the control group which cover approximately the same length of time. This is also true for the combined categories of improvement and no improvement. The low percentage of 19 for the combined categories of complete and social recovery at the time of discharge contrasts with higher percentages

reported by other investigators.² This may be explained by the fact that our patients were discharged three to four weeks after insulin treatment had been discontinued rather than kept in the hospital until they had reached the peak of their improvement. For the three and four year follow-up periods, the numbers of patients, 16 and 9, respectively, were too small for accurate comparison. This table seems to indicate that the remission rate for the various intervals from six months on were relatively stable for the duration of our follow-up period.

However, this does not mean that any given patient stays at a constant level of improvement. A separate analysis of the course of each patient was made through the successive follow-up periods. Twenty-one, or 32 per cent, of the patients maintained a fairly constant course. The condition of 20 patients, or 30 per cent, improved from

TABLE 3.—*Final Clinical Status of Patients Treated with Insulin Shock and of a Control Group at Last Follow-Up Period of From One to Four Years in Terms of Type of Onset*

Group	Onset	Total	Complete and Social Recovery	Improvement and No Improvement	Dead
Insulin	Acute.....	31 (47%)	14 (45%)	17 (55%)	
	Gradual.....	35 (53%)	9 (26%)	25 (72%)	1 (2%)
	Total.....	66 (100%)	23 (35%)	42 (64%)	1 (1%)
Control	Acute.....	31 (24%)	14 (45%)	17 (55%)	
	Gradual.....	101 (76%)	29 (29%)	68 (67%)	4 (4%)
	Total.....	132 (100%)	43 (33%)	85 (64%)	4 (3%)

the time of discharge to the final status; 10 patients, or 15 per cent, became worse. Fifteen patients, or 23 per cent, showed a fluctuating course of remissions and exacerbations. Eight of these 15 patients had the same status at the last follow-up period as at the time of discharge; 3 had become worse, and 4 had improved. From this it is evident that the course of schizophrenia after insulin therapy is a variable one.

Table 3 presents the clinical status at the last follow-up period of from one to four years for both the insulin and the control group in terms of type of onset. By acute onset is meant the sudden appearance

2. (a) Bond, E. D.: Continued Follow-Up Results in Insulin Shock Therapy and in Control Cases, *Am. J. Psychiat.* 97:1024-1028 (March) 1941. (b) The Treatment of Schizophrenia, Insulin Shock, Cardiazol and Sleep Treatment, Proceedings of the Eighty-Ninth Meeting of the Swiss Psychiatric Association at Münsingen, Berne, Switzerland, May 29-31, 1937, *ibid.* (supp.) 94:1-354 (May) 1938. Katzenelbogen, S.: A Critical Appraisal of the "Shock Therapies" in the Major Psychoses: Insulin, *Psychiatry* 2:493-505 (Nov.) 1939; 3:211-228 (May) 1940. Jessner, L., and Ryan, V. G.: Shock Treatment in Psychiatry, New York, Grune & Stratton, Inc., 1941.

of the fully developed psychosis, and by gradual onset is meant an insidious development of the psychosis. In each group there were 31 patients with acute onset, of which 14 patients, or 45 per cent, made either a complete or a social recovery. Of the patients with a gradual onset in the insulin series there were 35, of which 9, or 26 per cent, made a complete or a social recovery. This number is compared with 101 patients in the control group, of whom 29, or 29 per cent, attained a similar status. This implies that patients with an acute onset do not have a more favorable outcome when treated with insulin than when treated by conservative measures.

Table 4 shows the relationship between the clinical status at the last follow-up period and the duration of the illness. For both groups, of those patients ill less than six months, 44 per cent made a complete or

TABLE 4.—*Final Clinical Status of Patients Treated with Insulin Shock and of a Control Group at Last Follow-Up Period of From One to Four Years in Terms of Length of Illness Before Treatment*

Group	Duration of Illness	Total Number	Complete and Social Recovery	Improvement and No Improvement	Dead
Insulin	6 months.....	34 (52%)	15 (44%)	19 (56%)	
	7-18 months.....	14 (21%)	3 (21%)	10 (72%)	1 (7%)
	19 months and over.	18 (27%)	5 (28%)	13 (72%)	
	Total.....	66 (100%)	23 (35%)	42 (64%)	1 (1%)
Control	6 months.....	57 (43%)	25 (44%)	29 (51%)	3 (5%)
	7-18 months.....	26 (20%)	7 (27%)	19 (73%)	
	19 months and over.	49 (37%)	11 (22%)	37 (76%)	1 (2%)
	Total.....	132 (100%)	43 (33%)	85 (64%)	4 (3%)

a social recovery. Of those ill longer than six months, the decrease in the percentage who recovered was approximately the same in the two groups. These figures do not support the statement sometimes made^{2b} that early treatment of schizophrenia with insulin produces a higher rate of recovery than early treatment by other methods.

COMMENT

The data presented indicate that patients suffering from typical schizophrenia and treated by the insulin shock method as described did not have a better rate of recovery than those treated more conservatively.

The insulin shock technic employed differed from some of the methods used elsewhere.^{2b} Rivers and Bond³ contrasted two methods of insulin therapy—one similar to ours, in which the insulin was

3. Rivers, T. D., and Bond, E. D.: Follow-Up Results in Insulin Shock Therapy After One to Three Years, *Am. J. Psychiat.* 98:382-384 (Nov.) 1941.

decreased after coma levels were reached, and one in which insulin was increased. They reported that the latter method gave better results. It may be that differences in insulin shock technic yield different rates of remission.

In the comparison of the insulin-treated and the control group, it should be pointed out that the study was not strictly one of a group of schizophrenic patients treated with insulin and a group not treated at all. The patients constituting the control group were treated⁴ on the theory that they had problems and conflicts which they were unable to solve. These were considered important for their illnesses. An attempt was made to understand the development of their personalities, particularly the difficulties that they had encountered in their efforts at adjustment. With this knowledge, reconditioning and reeducation through the use of individualized socialization programs, on the one hand, and attempts to solve the conflicts by psychotherapy, on the other, were carried out. However, all the patients of the control group could not be subjected to this complete program, primarily owing to factors limiting their stay in the hospital: Eight, or 6 per cent, remained but two weeks; 31, or 24 per cent, three or four weeks; 37, or 29 per cent, five or six weeks; 20, or 15 per cent, seven or eight weeks; 16, or 12 per cent, nine to twelve weeks, and 20, or 15 per cent, more than three months. Some of these patients were transferred to state hospitals; none, however, received insulin shock therapy.

The similarity between the courses of the control and those of the insulin-treated patients suggests a common factor in the two methods of treatment. This factor may be that pressure toward socialization was being exerted constantly on the patients from several directions. The insulin shock treatment may be thought of as one method of exerting such pressure, especially through the attention the patient receives in experiencing the comas. Insulin shock, therefore, would not be considered a specific therapy for schizophrenia.

CONCLUSION

Sixty-six patients suffering from schizophrenia were given insulin shock therapy, and the results were compared with those for a group of 132 patients treated by conservative methods. Analysis of the subsequent courses for the two groups showed similar remission rates. Insulin shock therapy by the method described does not increase the remission rate of schizophrenia over that with more conservative methods of treatment.

Iowa State Psychopathic Hospital.

4. Malamud, W., and Miller, W. R.: Psychotherapy in Schizophrenias, *Am. J. Psychiat.* **11**:457-480 (Nov.) 1931.

STATISTICAL CONTROL STUDIES IN NEUROLOGY

I. THE BABINSKI SIGN

NATHAN SAVITSKY, M.D.

AND

M. J. MADONICK, M.D.

NEW YORK

We became interested in control studies in neurology while investigating the significance of objective signs in cases of head injury. It is evident that as a result of the medicolegal importance of many of these problems a great deal of emphasis is usually placed on objective signs. More weight is usually placed on a Babinski sign or an ocular muscle palsy than on the most intense subjective distress. We often wondered how many of these positive neurologic signs existed before the accident. The subject of the frequency of these signs in people who were not injured began to attract our attention. Considering the great number of injuries in large industrial organizations, it would be important to know the incidence of positive neurologic signs in control groups. Control groups do not necessarily imply normal people. In this study control groups refer to persons not under observation or treatment for head injuries or their sequelae.

We decided to determine, if possible, how scarred the population is from the neurologic standpoint. Old head injuries which were not considered serious, unrecognized complications of infectious childhood diseases, abortive forms of degenerative and heredofamilial diseases of the nervous system, mild cerebrovascular accidents with no gross paralyses are a few of the better known conditions which can cause a persistent Babinski sign without the person presenting complaints which would have called attention to the existence of these disorders. Older studies on the incidence of the Babinski sign are of little value because of the small number of cases usually investigated and because of various recent influences which, in our opinion, may tend to increase the incidence of the Babinski sign. One must recognize such factors as the increased frequency of virus diseases, the more widespread use of chemotherapy and spinal anesthesia and the notable rise in the number of industrial and traffic accidents, as well as the greater frequency of degenerative disease because of the increase in life expectancy.

Our data were gathered from three sources.

1. The first group consisted of 1,000 persons with head injuries seen in private practice. It is interesting to note the greater incidence

of males, 100 males to 63 females, which no doubt is due to the fact that the former are exposed to greater hazards, especially in the industrial fields.

2. The second series consisted of 2,500 patients admitted for general conditions to the wards of the Morrisania City Hospital. Patients with a condition suggesting a neurologic disease were excluded. The age curve for this series had a bell shape, indicating that we have probably taken a fair sample of the population. According to the fifteenth census of the population of the United States, 1930, the ratio of males to females in the County of the Bronx, New York city, was 100 to 100.6. In our series there were 100 males to 209 females. The greater proportion of females is accounted for to some degree by the large number of women with gynecologic conditions in the series. Negroes constitute 1.02 per cent of the population of the Bronx. In our series Negroes comprised 11.6 per cent of the patients examined. This large number is probably explained by the lower economic status of the race and the fact that the hospital is a city institution. The Chinese represented 0.023 per cent of the total non-Negro population in the Bronx. In our series the Chinese comprised 0.18 per cent of this population. Children below the age of 5 years were not included.

3. The third series, consisting of 704 inductees into the Army between the ages of 21 and 35, was a somewhat select group, since we did not see many who had been rejected by the local board physicians.

This paper is confined to a consideration of the Babinski sign. This sign was considered positive only when there was definite and constant extension of the large toe on plantar stimulation. The same stimulus was employed throughout to the outer part of the sole of the foot. Stimulation was adequate but not nocuous.

A positive Babinski sign was found in 4.3 per cent of the patients with head injuries and in 4.3 per cent of the hospital controls. The first 1,000 consecutive hospital controls showed an incidence of 4 per cent. There is no significant statistical difference between this 4 per cent and the 4.3 per cent of the group with head injuries. The actual difference between the two figures is less than three times the probable error. The relatively high incidence for the control group may be partly due to the large number of persons over 50 years of age. There were twice as many persons over 50 in the hospital control series as in the group with head injuries. The Babinski sign was nearly four times as frequent in persons over 50 as in those under 50 in the series of 2,500 control subjects. Syphilis played a small role in accounting for the Babinski sign. There was a slight difference in the incidence of positive serologic reactions of the blood between the 107 hospital patients with a positive Babinski sign and a similar number of patients of approximately the

same age distribution without a Babinski sign. There was no significant increase in the incidence of positive Babinski signs in those with positive serologic reactions.

Further confirmation of the theory that age is a factor was the observation that 1.15 per cent of the hospital controls between 21 and 35 years of age (781 cases) and 1.25 per cent of the 704 inductees had a positive Babinski sign. The closeness of the figures obtained is additional evidence that we were dealing with random samples.

The literature reveals few similar studies on large numbers of people. Schüler¹ found extension, notably of the big toe, in 8 per cent of normal men and in 4 per cent of normal women. Cohn² described extension of the great toe, with either flexion or extension of the other toes, in 20 per cent of the cases in a series. Neither of these investigators indicated the number of persons examined. Collier³ examined 100 adults in the medical wards of a general hospital who were free from acute disease and presented no sign of any lesion of the nervous system. There was no dorsioextensor response in any instance. Walton and Paul⁴ did not elicit the sign in a group of 100 adult patients who were not suffering from any nervous disorders and in a group of 100 students at a girls' school. Prince,⁵ in examining presumably healthy men between 22 and 33 years of age for civil service tests, found that the sign occurred in 1 of 156 persons. Davidson⁶ examined 161 adults; 151 had non-neurologic or orthopedic spinal conditions, and 10 were medical students. He stated that isolated extension of the big toe with fanning of the other toes does not occur in normal adults. Three per cent showed extension of the big toe, with extension of the little toes as well. Yakovlev and Farrell⁷ found a Babinski sign in 1 of 168 college students in a camp for the Reserve Officers' Training Corps.

1. Schüler, L.: Beobachtungen über Zehenreflexe, *Neurol. Centralbl.* **18**:585, 1899.

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In the tabulation are indicated various factors reported in the literature which can cause the appearance of a fleeting Babinski sign. There were 28 patients with heart failure in the hospital series who had a positive Babinski sign. None of the other exciting factors listed were present. These variables must be borne in mind in making such control studies.

EXCITING FACTOR	AUTHOR
Exercise—14 mile (22.5 kilometer) march	Yakovlev and Farrell ⁷
Stay in bed for months or years.....	Sehestedt ^{7a}
Freezing (cryotherapy).....	Davis ⁸
Sleep	Hawthorne ⁹ ; Rosett ¹⁰ ; Kleitman ¹¹
Cheyne-Stokes breathing during apnea.....	Tournay ¹² ; Monier-Vinard ¹³
Cardiac insufficiency.....	Lhermitte and Dupont ¹⁴ ; Gondet ¹⁵
Jaundice; hepatitis.....	Rolleston ¹⁶
Hypoglycemia (spontaneous).....	Feinier, Soltz and Haun ¹⁷
Hypoglycemia (overdose of insulin).....	Andersen ¹⁸
Hypoglycemia (induced in psychosis).....	Heiman ¹⁹ ; Hoch ²⁰
Opium	Walton and Paul ⁴
Delayed chloroform, sulfonal (diethylsulfone-dimethylmethane), coal gas (carbon monoxide) and other poisoning.....	Elliott and Walshe ²¹
Scopolamine	Zador ²² ; Rosenfeld ²³
Amytal	Thorner ²⁴
Barbiturates	Ironsides ²⁵
Carbon disulfide	Lewy ²⁷
Gasoline intoxication	Machle ²⁸
Nitrous oxide asphyxia.....	Courville ²⁹
Lead	Abraham and Baird ³⁰
Strychnine	Babinski, quoted by Gondet ¹⁵
Paraldehyde	Personal experience
Vertigo	Berggren ³¹

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SUMMARY

The incidence of the Babinski sign was studied in three groups of subjects: (a) 2,500 patients with non-neurologic conditions admitted to a general hospital; (b) 1,000 patients with head injuries, and (c) 704 inductees into the Army.

Four and three-tenths per cent of patients in the first and second group had a positive Babinski sign.

The Babinski sign was found in 1.15 per cent of the hospital control series, who were between the ages of 21 and 35 years, and in 1.27 per cent of the inductees, of the same age distribution.

In the hospital series the Babinski sign was nearly twice as frequent in persons over 50 as in those under 50 years of age.

Various factors which may produce a transitory Babinski sign are listed.

1882 Grand Concourse.

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Case Reports

ABERRANT THYROID TUMOR OF THE VERTEBRAE WITH COMPRESSION OF THE SPINAL CORD

Recovery After Operation and High Voltage .
Roentgen Therapy

PETER G. DENKER, M.D.

Associate Attending Neuropsychiatrist, Bellevue Hospital

AND

RAYMOND L. OSBORNE, M.D.

Resident Neurologist, Bellevue Hospital

NEW YORK

We report an unusual case of vertebral tumor composed of normal thyroid tissue, with secondary compression of the cord. We have been unable to find an exactly similar case reported in the literature. Of special interest is the fact that complete recovery was obtained after operation and high voltage roentgen therapy.

REPORT OF A CASE

History.—F. G., a 27 year old, married, Italian-born post office clerk, was first admitted to the neurologic service of Bellevue Hospital on Sept. 7, 1932, with the following complaints: (1) progressive weakness of the legs for the preceding five months, at first noticed as a feeling of heaviness while running; (2) involuntary jerkings of his legs for the previous four months, worse in the right leg; (3) subjective feelings of numbness and tightness for the previous three months, at first noted in the left knee but soon followed by similar sensations in the right knee, with gradual extension up the body to the level of the chest; (4) urinary disturbances of five months' duration, initially in the nature of retardation of flow, followed two months before admission by a "drawn feeling like electricity" in both legs while voiding; (5) loss of libido of one month's duration, with sensations during orgasm similar to those experienced while voiding, and (6) pain in the lower thoracic portion of the spine for the previous month.

The only significant events in his past history were tonsillectomy one year before admission and herniorrhaphy eight years previously.

Physical Examination.—The results of examination were without significance except for the neurologic signs. The cranial nerves were normal. Sensory examination revealed hypalgesia and hypesthesia below the fourth thoracic level and loss of position sense in the toes. There was no deep pain when the achilles tendons were squeezed. Vibration sense was lost in the legs, and the sacral region was spared. Both lower extremities were spastic, with marked weakness. There was ataxia in the heel to knee test; all the deep reflexes of the legs were hyperactive, with bilateral ankle clonus; the Babinski sign was present bilaterally, and the abdominal and cremasteric reflexes were absent. There was tenderness on pressure over the third dorsal spine.

Laboratory Data.—The blood count revealed 4,360,000 red blood cells per cubic millimeter, 80 per cent hemoglobin (100 per cent is equivalent to 14.5 Gm. per hundred cubic centimeters) and 10,500 white blood cells per cubic millimeter, the

From the Neurological and Neurosurgical Service (Second Medical Division, Cornell University Medical College), Bellevue Hospital; Dr. Foster Kennedy, Chief of Service.

smear and the differential count being normal. The nonprotein nitrogen of the blood measured 30 mg. per hundred cubic centimeters and the blood sugar 92 mg. A culture of the blood was sterile; the Wassermann reaction of the blood was negative, and the basal metabolic rate was plus 14.8 per cent.

Roentgenograms of the spine showed some erosion of the transverse processes of the third thoracic vertebra, with no evident involvement of the vertebral body. Fluoroscopic examination showed nothing abnormal.

Lumbar puncture revealed a clear, colorless spinal fluid; the initial pressure was 180 mm. of water, and there was a complete manometric block on jugular compression. The cell count of the spinal fluid was 6 lymphocytes per cubic millimeter; the Wassermann reaction was negative, and the colloidal gold curve was 0000000000.

Operation.—Laminectomy was performed on September 28. The spinous processes of the third to the fifth thoracic vertebrae inclusive were exposed, which revealed a soft tumor involving and partially destroying these processes as well as the laminae of the second and third thoracic vertebrae. The tumor was described as pink, with the consistency of bone marrow, infiltrating and very vascular, with a tendency to bleed profusely wherever it was touched. The dura was not opened.

Pathologic Report.—The specimen of tumor tissue removed at operation consisted of "apparently normal thyroid tissue, with high alveolar epithelium and no evidence of malignancy. It undoubtedly represented aberrant thyroid tissue."

Postoperative Treatment.—After operation the affected vertebrae were treated with high voltage roentgen therapy, with gradual improvement. Examination on Nov. 6, 1932 revealed slight increase in the strength of the legs and some diminution in the sensory disturbance. Delay in starting the urinary stream was no longer present. The patient was discharged from the hospital on Dec. 9, 1932, improved.

Subsequent Course.—In August 1933 the patient returned to the neurologic clinic complaining of recurrence of the weakness in his legs and mild paresthesias in both feet. Neurologic examination at this time revealed a sensory level up to the fourth thoracic segment, with weakness of the legs. Ankle clonus and the Babinski sign were elicited bilaterally. The abdominal reflexes were absent. In short, there was recurrence of the original signs and symptoms. The patient was therefore readmitted to the neurologic service on Sept. 28, 1933.

On admission, neurologic examination revealed the same changes as those noted in September 1932, on his first admission. Lumbar puncture was again performed; the fluid was clear and colorless, with a partial manometric block and a total protein content of 100 mg. per hundred cubic centimeters. Neurosurgical consultation was requested, and operation was pronounced inadvisable. He was therefore given another course of high voltage roentgen treatments and discharged on Nov. 16, 1933, unimproved.

On Jan. 4, 1934 the patient was readmitted for the third time, complaining of a progressive downhill course since his previous admission. He had become more paralyzed and was bedridden. There was difficulty in starting the urinary stream. No symptoms of goiter or hyperthyroidism were observed on this or any other examination. The neurologic findings were again essentially similar to those on his original admission except that the paraplegia had become gradually more severe. Radiation therapy was again resorted to. Over the next few months no noticeable improvement occurred, and the patient remained bedridden.

The entire case was reviewed, and the absence of improvement, with the persistence of manometric block, seemed to warrant surgical reexploration. On May 17, 1934 laminectomy was therefore again performed. The previous scar was excised; the fascia and muscles were split, and the tumor was exposed.

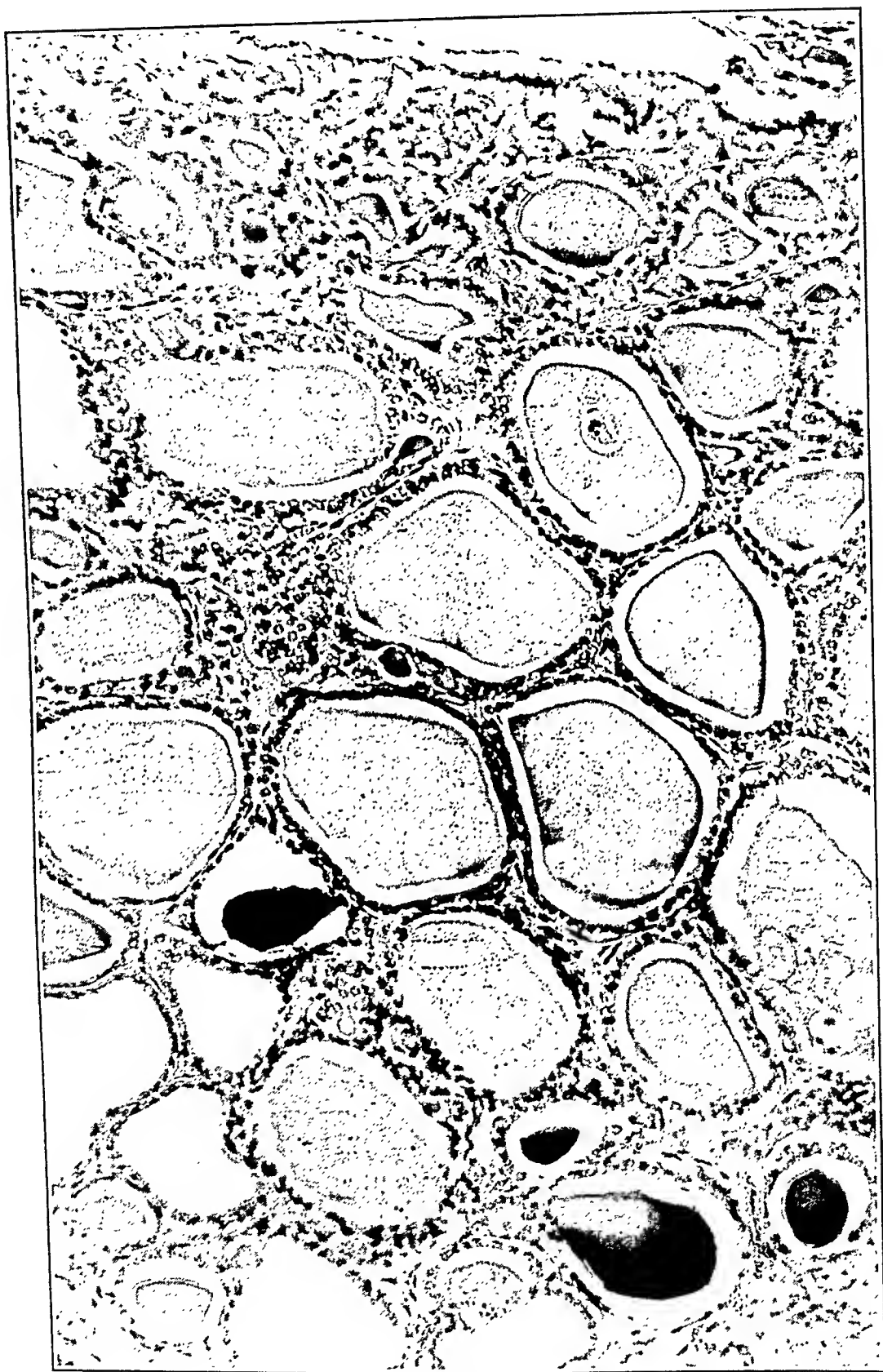


Fig. 1.—Portion of tumor tissue; $\times 192$.

The growth was composed of reddish brown, soft tissue resembling normal thyroid in consistency and appearance. A large portion was removed with the curet. Because the tumor tissue had extended into the body of the fifth thoracic



Fig. 2.—Higher magnification of a portion of the tumor tissue shown in figure 1; $\times 736$.

vertebra, total removal was considered inadvisable. Pathologic study of this specimen of tumor revealed well preserved, normal thyroid tissue, which was not malignant.

After the second operation high voltage roentgen therapy was again instituted and continued over the next six months. Gradual improvement in the clinical

status occurred. At the time of discharge, in December 1934, the patient was able to walk and void normally, and only minimal sensory changes remained.

Since then he has been observed periodically and has had repeated neurologic examinations. At present, in January 1943, he has no subjective complaints; the neurologic status is normal, and the patient has been back at his usual employment as a post office clerk for the past eight years.

COMMENT

We believe that this case is unique in that (1) complete recovery has been obtained and the patient has been entirely well without further therapy for nine years, and (2) no tumor of the thyroid gland or any symptom of hyperthyroidism has ever been observed in this case. In view of the long period of observation (ten years), as well as the absence of signs of malignancy in the histologic sections of the tumor itself, one can rule out a metastatic carcinoma from the thyroid gland. It is therefore necessary in this case to assume that the spinal tumor originated either from aberrant thyroid tissue or from dislodged cells of normal thyroid tissue, the so-called benign thyroid metastasis. The latter condition of benign metastasis is one of extremely difficult definition. Ewing,¹ in discussing thyroid metastasis to the spine, pointed out that the tumor reproduces thyroid tissue with fidelity but that in most recorded cases, though the thyroid tissue itself is considered benign, the secondary deposits usually become malignant. This obviously did not occur in our case, possibly owing to the beneficial effects of the high voltage roentgen therapy. It should be recalled that the entire tumor mass was not removed surgically because of the extensive involvement of bone. No additional roentgen therapy has been administered since December 1934; yet no evidence of recurrence locally or in any other organ of the body has been noted. It therefore seems most logical to ascribe the lesion in our case to hyperplasia of aberrant thyroid tissue.

SUMMARY AND CONCLUSIONS

A case of aberrant thyroid tumor of the vertebrae with compression of the spinal cord and complete recovery following operation and high voltage roentgen therapy is reported.

The possible histogenesis is discussed.

The beneficial effect of high voltage roentgen therapy on such a lesion is stressed.

It is reasonable to assume, from the ten years of follow-up observation, that complete recovery has occurred.

No similar case of aberrant or benign metastatic thyroid lesion of the spine with complete recovery has been found in a review of the literature.

140 East Fifty-Fourth Street.

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News and Comment

COMMITTEE ON WAR PSYCHIATRY OF THE AMERICAN PSYCHIATRIC ASSOCIATION

The Committee on War Psychiatry of the American Psychiatric Association has published a study dealing with the steps which have been taken for the maintenance and improvement of civilian mental health in various types of communities throughout the country. The procedures used in state-wide areas, large cities and metropolitan districts and in small towns and rural areas have been assembled, and their fundamental principles have been described.

This publication may be obtained without cost on application. More detailed information on particular aspects of civilian mental health may be secured on request. Such material for rural areas may be obtained from Dr. T. Raphael, University of Michigan, Ann Arbor, Mich.; for state-wide areas from Dr. F. H. Sleeper, 100 Nashua Street, Boston, and for large cities and metropolitan areas from Dr. D. Ewen Cameron, Albany Hospital, Albany, N. Y.

TOPEKA INSTITUTE FOR PSYCHOANALYSIS

The Topeka Institute for Psychoanalysis, which has since 1938 acted as a branch of the Chicago Institute for Psychoanalysis, has been authorized to function as an independent institute by the American Psychoanalytic Association and its constituent societies.

The aim of the Topeka Institute is primarily the training of physicians in the theory and practice of psychoanalysis; secondarily it aims to promote an adequate knowledge of psychoanalysis among members of professions with problems related to psychoanalysis, such as general medical men, psychiatric nurses, social workers and teachers.

In its curriculum for physicians the institute intends to provide, in addition to preparatory analyses, a complete program of psychoanalytic instruction covering all requirements laid down in the "Minimal Standards for the Training of Physicians in Psychoanalysis" of the American Psychoanalytic Association. In order to fulfil this, a three year period of theoretic instruction is regarded as necessary.

The institute will operate in three places: Topeka, Kan.; Los Angeles, and San Francisco.

AMERICAN BOARD OF NEUROLOGICAL SURGERY

The next examination of the American Board of Neurological Surgery will be held in Chicago, at the Illinois Neuropsychiatric Institute, on Feb. 15 and 16, 1943.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

STRUCTURES OF THE NEUROHYPOPHYSIS WITH SPECIAL REFERENCE TO NERVE ENDINGS. E. VAZQUEZ-LOPEZ, *BRAIN* 65:1, 1942.

This investigation deals with the manner in which nerve fibers end in the hypophysis. It was made chiefly on frozen sections of the pituitary gland of the horse, some studies also being made on the ox, sheep, rabbit, guinea pig and rat. Nerve fibers were stained by silver and gold impregnation methods, various technics being followed in order to assure proper differentiation of connective tissue, nerve fibers and neuroglial prolongations.

Nerve fibers to the hypophysis arise in hypothalamic nuclei, pass through the eminentia media of the tuber cinereum and enter the stalk grouped together in thick, close-set bundles. As they enter the pars nervosa, they fan out, and toward the distal portion they form a dense network of fibers running in all directions. Many of these fibers end in the perivascular spaces formed by the neuroglia around the blood vessels of the neurohypophysis. In this acellular area, the nerve fibers are seen to form extensive arborizations, including various swellings, clubbings and meniscuses. This typical nerve ending apparatus in relation to the blood vessels is present in a profusion such as is rarely equaled elsewhere in the body.

A second group of fibers enters the pars intermedia, where it appears to come into direct contact with the epithelial cells of the region and to form expansions and other structures, suggesting that the nerve fibers end among these cells. Actual pericellular plexuses were not observed. A third group of fibers, in the most distal portion of the gland, forms a system of nerve bundles lying beneath the connective tissue capsule of the pars nervosa and ends in relation to special meningeal corpuscles which lie embedded in the thick fibrous covering of the apical region.

The nerve fibers and nerve endings innervating the meningeal corpuscles are similar morphologically to those ending in the perivascular networks, suggesting a similar function. The meningeal corpuscles appear to have only a sensory function. Furthermore, the morphologic appearance of the nerve endings in the perivascular spaces suggests a close relationship to perivascular nerve endings of a sensory character present in other parts of the body. These facts indicate that the great mass of the neurohypophysis consists of sensory elements and that the main function of the organ must be that of a gigantic perivascular receptive apparatus. Vazquez-Lopez suggests that this sensory system may consist of chemoreceptors and pressoreceptors concerned with regulation of metabolic and hormonal functions. This regulation is mediated through the diencephalic centers in which the nerve fibers to the neurohypophysis originate.

MASLAND, Philadelphia.

THE PRESENCE AND LOCALIZATION OF VITAMIN C IN THE CENTRAL NERVOUS SYSTEM. G. WOLF-HEIDEGGER, *Confinia neurol.* 4:121, 1942.

The author studied the presence and localization of vitamin C in the brains of rats and of normal and scorbutic guinea pigs by the use of the histochemical method of Giroud-Leblond. By this method the silver granules indicating the presence of ascorbic acid could be seen in the various types of nerve cells in all the regions of the brains of rats and normal guinea pigs. These granules were noted only in the cell plasma, never in the nuclei. In the pyramidal cells the granules were present in the cone of origin and in the proximal portion of the

axon. Microglia and oligodendroglia showed a definite vitamin C reaction. No evidence of vitamin C was observed in the cells of the choroid plexus. The ependymal cells were free from granules. The peripheral nerves gave no vitamin C reaction. In scorbutic guinea pigs none of the investigated portions of the nervous system showed a positive reaction for vitamin C. DeJONG, Ann Arbor, Mich.

Physiology and Biochemistry

THE NORMAL RATE OF REDUCTION OF METHEMOGLOBIN IN DOGS. WILLIAM W. COX and WILLIAM B. WENDEL, J. Biol. Chem. **143**:331, 1942.

Methemoglobin contained within circulating erythrocytes of dogs is reduced to hemoglobin at a constant average rate of 11.3 per cent of the total pigment per hour. This rate, therefore, represents the maximum resistance of this species to accumulation of methemoglobin. Reduction of intracorpuseular methemoglobin is solely a function of enzyme systems contained within the erythrocytes. Ability to reduce methemoglobin is impaired by low body temperature. It is not affected by severe hypoglycemia or by blood sugar concentrations several times the normal. Capacity to convert methemoglobin to hemoglobin is not diminished even after all the blood pigment has been converted to methemoglobin four times in a relatively short period.

PAGE, Indianapolis.

THE IN VITRO FORMATION OF PHOSPHOLIPID BY BRAIN AND NERVE WITH RADIOACTIVE PHOSPHORUS AS INDICATOR. B. A. FRIES, H. SCHACHNER and I. L. CHAIKOFF, J. Biol. Chem. **144**:59, 1942.

In vivo experiments with radioactive phosphorus have clearly established that liver and small intestine are organs in which phosphatide metabolism is great, while in brain it is low. The question arises whether nerve tissue can synthesize phosphatide or must acquire it from plasma. The authors have demonstrated that excised brain of young and old rats and nerve of dog form phosphatide in vitro. Slices as well as homogenate form it.

PAGE, Indianapolis.

THE BEHAVIOR OF LIPIDS DURING AUTOLYSIS OF LIVER AND BRAIN. W. M. SPERRY, F. C. BRAND and W. M. COPENHAVER, J. Biol. Chem. **144**:297, 1942.

Neither cholesterol nor phosphatides change in brain or liver when autolysis occurs. They become concentrated because of the large loss of tissue during autolysis. Cholesterol is similarly concentrated in liver left free in the abdominal cavity.

PAGE, Indianapolis.

ARTERIAL AND CEREBRAL VENOUS BLOOD: ARTERIAL-VENOUS DIFFERENCES IN MAN. E. L. GIBBS, W. G. LENNOX, L. F. NIMS and F. A. GIBBS, J. Biol. Chem. **144**:325, 1942.

The determinations of oxygen, carbon dioxide, p_{H} , lactic acid, sugar, total base and inorganic phosphorus have been measured on the arterial and the internal jugular venous blood of 50 intelligent, healthy young men with normal electroencephalograms. Samples of blood from an artery and the internal jugular vein were drawn simultaneously, thus permitting estimation of the metabolic activity of the brain. These data furnish normal control data for future studies of the metabolism of brains which are functioning abnormally. The respiratory quotient of the brain in this series was 0.99. This figure, together with data on the concentrations of sugar, lactic acid and oxygen in the blood entering and leaving the brain, indicates that sugar is the principal source of energy for the brain in vivo. However, not all the sugar is completely oxidized, for a small part appears to be converted into lactic acid.

PAGE, Indianapolis.

A STUDY OF THE NITROGENOUS CONSTITUENTS OF TISSUE PHOSPHATIDES. E. CHARGAFF, M. ZIFF and D. RITTENBERG, *J. Biol. Chem.* **144**:343, 1942.

The distribution of ethanolamine and choline in partially purified phosphatides from liver, brain and heart was determined by the method of isotope dilution with N^{15} . The amino acid content of these phosphatides, as well as of samples from lung and egg yolk, was likewise determined. In a preparation of pig liver phosphatides 35.6 per cent of the amino nitrogen could not be characterized either as ethanolamine or as amino acid. All of the nonamino nitrogen in a hydrolyzate of this phosphatide was found to be present as choline. In a preparation of beef brain phosphatides all the amino nitrogen could be identified as ethanolamine and amino acid, whereas only 50 per cent of the nonamino nitrogen was accounted for as choline. In a preparation of pig heart phosphatides 86.8 per cent of the amino nitrogen was accounted for as ethanolamine and amino acid, and only 49.3 per cent of the nonamino nitrogen could be characterized as choline. The phosphatides from brain and lung were found to have the highest amino acid content. The egg yolk phosphatides were free of amino acid. Data on the effect of storage on phospholipid composition and a discussion of some of the implications of the experimental results are included.

PAGE, Indianapolis.

CURE OF PARALYSIS IN RATS WITH BIOTIN CONCENTRATES AND CRYSTALLINE BIOTIN. E. NIELSEN and C. A. ELVEHJEM, *J. Biol. Chem.* **144**:405, 1942.

In a previous paper Nielsen and Elvehjem showed that a "spectacle eye condition" in rats, produced by the addition of 10 per cent egg white to a purified ration containing synthetic B complex vitamins, could be prevented and cured by the addition of biotin. If the rats were continued on the egg white ration for six to eight weeks after the "spectacle eye" symptom appeared, typical paralysis or spasticity of the hindlegs developed. The administration of biotin concentrates or biotin is specific for this syndrome. High levels of fat in the diet slightly prolong the onset of paralysis. Riboflavin, pyridoxine or the combination of the two vitamins was without effect. High creatine levels were observed in the leg muscles of paralytic rats.

PAGE, Indianapolis.

OCCURRENCE OF SPHINGOMYELIN IN TISSUES OF THE CAT. F. E. HUNTER, *J. Biol. Chem.* **144**:439, 1942.

Although the presence in tissues of at least three different phospholipids has been known for many years, the methods available limited earlier studies chiefly to the total phospholipid fraction in various tissues. Only in recent years have detailed studies concerning the lecithins and cephalins appeared and added to knowledge of their possible functions. Considerably less is known concerning the phospholipid sphingomyelin. The sphingomyelin concentration found in eleven tissues from cats varied from 0.075 per cent, in skeletal muscle, to 1.25 per cent, in the brain. The proportion of sphingomyelin in the total phospholipid ranged from 7.5 to 33.2 per cent, so that there was no correlation between sphingomyelin and total phospholipid. The values are compared with those found for tissues from other species by previous workers. Some possible relation of sphingomyelin to fat metabolism and special properties or functions of tissues are discussed.

PAGE, Indianapolis.

THE PYRAMIDAL TRACT: THE EFFECT OF PRE- AND POSTCENTRAL CORTICAL LESIONS ON THE FIBER COMPONENTS OF THE PYRAMIDS IN MONKEY. A. M. LASSEK, *J. Nerv. & Ment. Dis.* **95**:721 (June) 1942.

Lassek believes that there is no convincing proof that destruction of area 4 causes complete degeneration of the axis-cylinders within the pyramids of the medulla oblongata in primates or in other mammals. In this investigation he studied the effect on the fiber components of the pyramids of extirpations of the

precentral and postcentral cortex, using a refined silver stain as a criterion of fiber loss.

The left cerebral cortex in each of 6 monkeys was operated on; in 3 animals the motor cortex (area 4) was removed, in 1 the postcentral gyrus and adjacent portion of the parietal lobe were extirpated and in 2 combined lesions of the central gyri were made. After from nine to eighteen weeks selected sections were taken from both sides of the mesencephalon, the pons, the medulla and each of the four regions of the cord, embedded in paraffin and stained with protargol (protein silver). In each specimen the pyramids of the normal and the experimental side were measured for square area and the fiber components were compared.

Extirpation of the Betz cell region (area 4) caused degeneration of only a portion of the fibers within the pyramid. In a typical monkey the affected pyramid was 13 per cent smaller than normal and possessed 68 per cent as many axicylinders. More extensive lesions extending in front of and behind the central sulcus failed to cause complete degeneration of the pyramids, and it is the impression of the author that the parietal cortex contributes few, if any, fibers to the pyramidal system. In none of the medullas of the 6 monkeys could any trace be found of either a circumolivary or a recurrent Pick's bundle, and no evidence of a ventral corticospinal tract was seen in the spinal cords.

Lassek's observation that about two thirds of the pyramidal fibers were intact after destruction of area 4 is in accord with the results of other investigators on the rabbit, cat, monkey and dog. The fibers lost were mainly of the large myelinated type. The view that the Betz cells give sole origin to the fibers of the pyramidal tract has been based almost entirely on results drawn from retrograde experiments, and the author questions the validity of these conclusions for several reasons. Furthermore, numerical studies have shown that the large motor cells of area 4 could not possibly account for more than 2 or 3 per cent of the fibers within the pyramids. It is difficult to see how the large Betz cells could give origin to the small myelinated and unmyelinated fibers which comprise a substantial portion of the pyramids.

CHODOFF, Langley Field, Va.

EFFECT OF ALKALOSIS AND ACIDOSIS ON CORTICAL ELECTRICAL ACTIVITY AND BLOOD FLOW. ALBERT J. LUBIN and J. C. PRICE, *J. Neurophysiol.* 5:261, 1942.

It has been generally believed that changes in cortical potentials associated with variations in carbon dioxide tension have been the result of the concomitant "alkalosis" and "acidosis." In these experiments on 12 cats, intravenous injections of hydrochloric acid and of sodium carbonate sufficiently large to alter the respiratory rate failed to disturb the cortical potentials significantly. The authors suggest that changes produced by increasing or decreasing the carbon dioxide tension of the blood are related to the effect of carbon dioxide itself rather than to the resultant change in hydrogen ion concentration of either the blood or the tissues.

Effects on the pial arteries were photographed through a lucite window in the skull of each animal. The acid tended to dilate the capillaries and the base to constrict them. There was no apparent relationship between these changes and the cortical potentials.

DRAYER, Philadelphia.

ORIGIN, CONDUCTION AND TERMINATION OF IMPULSES IN DORSAL SPINOCEREBELLAR TRACTS OF CATS. HARRY GRUNDFEST and BERRY CAMPBELL, *J. Neurophysiol.* 5:275, 1942.

Grundfest and Campbell studied electrical activity along the dorsal spinocerebellar tract of cats. Stimuli were delivered to peripheral nerves of the hindlimbs and to the tract itself. Contralateral stimuli evoked no impulses. The fibers in this tract are larger than those in the fasciculus gracilis, and impulses travel along it nearly twice as rapidly. There is a delay of five-tenths to nine-tenths millisecond, after the primary impulses arrive in the collaterals to Clarke's column, but the difference in rate of travel allows the impulses along Flechsig's tract to

reach the medulla more than one millisecond earlier than the corresponding impulses along the fasciculus gracilis.

Conditioning by stimulation of other afferent pathways was observed. "The electrical data indicate that the cells of origin of the fibers of the tract receive collaterals from more than one primary sensory neuron, and evidence also points to their activation by internuncial chains of varying degrees of complexity."

Responses in the cerebellar cortex were considerable. The early components were found to be "largely or entirely due to the mediation of impulses from Flechsig's tract."

DRAYER, Philadelphia.

INTERFERENCE FACTORS IN DELAYED RESPONSE IN MONKEYS AFTER REMOVAL OF FRONTAL LOBES. ROBERT B. MALMO, *J. Neurophysiol.* 5:295, 1942.

After bilateral removal of the frontal association areas, monkeys succeeded in delayed response performance when darkness was maintained during the delay interval. Unlike normal animals, however, these animals failed in the test when a bright light was turned on in the cage during the delay interval. The indirect method of delayed response was used throughout the experiment; that is, light instead of food was used as the cue stimulus.

These results make necessary the revision of previous theories concerning the functions of the frontal association areas. The hypothesis is suggested that removal of the frontal association areas in primates leads to impairment in the general capacity for memory, because the loss of these areas renders them more susceptible to retroactive inhibition.

DRAYER, Philadelphia.

OBSERVATIONS IN HYPOGLYCAEMIA: III. C. S. F. SUGAR AND COMA. W. MAYER-GROSS and F. BERLINER, *J. Ment. Sc.* 88:82, 1942.

These studies were based on determinations of sugar in 35 specimens of cerebrospinal fluid obtained from 6 patients. To avoid the influence on the blood sugar of the stimulus of the lumbar puncture, samples of blood were generally taken ten to twenty minutes before the spinal puncture and the sugar levels of these specimens determined. The sugar curves for the two mediums tended to be parallel, with some delay in the increase of the cerebrospinal sugar. In these cases hypoglycemic coma was no more dependent on a low sugar level in the cerebrospinal fluid than it was on a low level in the blood.

DRAYER, Philadelphia.

FURTHER OBSERVATIONS ON SODIUM AMYTAL EXPERIMENTS. F. REITMANN, *J. Ment. Sc.* 88:122, 1942.

The experiments reported in this paper deal with the reactions of 30 psychiatric patients, chiefly neurotic to intravenous injections of sodium amytal. The effects on the blood sugar levels were studied. It was found that the psychologic effects of sodium amytal were accompanied by slight hyperglycemia. In some cases there was temporary depression of the dextrose tolerance curve. The author suggests that these facts are in support of the belief that sodium amytal has a direct action on the hypothalamic centers, and does not simply release these nuclei by depression of the cortex.

DRAYER, Philadelphia.

Neuropathology

SUPRASELLAR TUMORS RELATED TO THE PARS INTERMEDIA OF THE HYPOPHYSIS. W. G. MACCALLUM, *Arch. Path.* 34:13 (July) 1942.

In the adult the cells of the pars intermedia can be distinguished from those of the more specialized anterior lobe. Its cells are often in irregular clumps, frequently forming small cysts with a colloid content. Occasionally the lining cells present a more cylindric form with some evidence of cilia on their free surfaces.

Often the cells extend into the posterior lobe and are scattered along the stalk up to the base of the third ventricle, where they are closely connected with the pars tuberalis.

The tumor from these cells forms a mass which extends above the diaphragma sellae, although it may extend down and compress the hypophysis and partially surround its stalk. The further growth, within a capsule, projects upward and forward so as to compress the optic chiasm and one or both optic nerves; thence it extends into the floor of the third ventricle and upward so as to occupy the cavity of the latter and destroy the fornix and surrounding structures.

The symptoms produced are almost identical in all cases: bilateral hemianopia and often complete blindness in one eye, weakness, loss of libido and beginning obesity.

The surgical treatment has consisted of incision into the capsule and curetting of the contents.

Microscopically the cells are alike throughout. They tend to be cylindric, around capillaries, and often there are slightly irregular spaces between the strands of such cells. No stain brings out anything specific in the nature of granules. The tumor must be distinguished from chromophobe adenoma of the hypophysis. Usually the lesion is located within the anterior lobe, seldom reaching the capsule.

The author has suggested that the Cushing syndrome is due to a nodule of pars intermedia within the anterior lobe, but this has been "violently contradicted."

WINKELMAN, Philadelphia.

FIBROSARCOMA OF ARACHNOIDAL ORIGIN WITH METASTASES. WILLIAM O. RUSSELL and ERNEST SACHS, *Arch. Path.* 34:240 (July) 1942.

Russell and Sachs report 4 cases of a malignant intracranial tumor believed to have its origin in arachnoidal cells. Only 4 cases of a similar kind were found in the literature. Of the authors' 4 cases, metastases into distant organs occurred in 3, and in the fourth case invasion of blood vessels by tumor suggested metastases, but these could not be found.

The tumors were closely related to arachnoidal fibroblastoma but were characteristic of fibrosarcoma, a malignant mesodermal tumor showing a type cell which resembled a fibroblast and produced collagen and reticulum. The authors suggest the term arachnoidal fibrosarcoma for this type of lesion.

Only 1 case need be cited. In a woman of 38, who had had an intracranial tumor removed thirteen years before, abdominal symptoms developed. At operation the surface of the liver was observed to be "covered with grayish white nodules of tumor." The histopathologic diagnosis was fibrosarcoma. The hepatic lesion was considered to have metastasized from the original cerebral tumor.

WINKELMAN, Philadelphia.

ENCEPHALOMALACIA WITH CAVITY FORMATION IN INFANTS. LEWIS D. STEVENSON and LILLIAN E. MCGOWAN, *Arch. Path.* 34:286 (July) 1942.

Stevenson and McGowan describe their observations on 7 infants with what they term "encephalomalacia with cavity formation," mainly within the white matter. The cause is unknown; in 3 of their cases the Wassermann reaction was positive. The condition does not depend on thrombosis of venous sinuses, on an arterial abnormality of the brain or on encephalitis.

It was present at birth, and the clinical picture developed shortly thereafter. There is no characteristic clinical syndrome, but the condition can be diagnosed during the life of the infant by encephalogram, which shows enlargement of the ventricles and in many cases filling of the subcortical cavities with air.

WINKELMAN, Philadelphia.

A CIRCUMSCRIBED ARACHNOID SARCOMA OF THE CEREBELLUM. B. MARQUARDT, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **171**:117 (Feb.) 1941.

The author adds a fourth case of arachnoid sarcoma to 3 previously reported by Foerster and Gagel. The patient, a 43 year old woman, had a sudden onset of the illness, with severe occipital headaches. These disappeared but recurred about a month later, with intensification of the pain on bending. They were not relieved by lying down. Dizziness and occasional nausea were noted when she was off the bed. About four months after the onset she lost consciousness a few hours after a skiing accident. The next day the occipital headache recurred. Shortly before admission her gait was noted as unsteady. On admission she complained of pain in the head on moving it backward; she held her head stiffly; there was slight nystagmus on right horizontal gaze; the edge of the left disk was blurred; there were mild ataxia in the finger to nose test on the left side and some unsteadiness in the heel to knee tests; she fell backward and to the left in the Romberg test. A ventriculogram showed pronounced internal hydrocephalus with dilatation of the third ventricle. The fourth ventricle and the aqueduct of Sylvius were not seen. Death followed operation.

A soft white tumor, the size of a plum, was observed in the region of the vermis. The cerebellum was indented at the site of the tumor, which was readily removed. The meninges around the tumor seemed thickened. Histologic examination revealed a sarcoma with extension of the tumor tissue into the cerebellar cortex. Two types of cells were seen—a smaller, deeply staining lymphocyte-like cell, with a poorly delineated nucleus and cell membrane, and a larger, poorly staining, oval cell, with a clear nucleus and cell membrane. These cells showed a tendency to infiltrate the adventitial layer only. Differential stains showed no glia cells or fibers and no ganglion cells or axis-cylinders. There were no gitter cells. Reticular fibers were present.

SAVITSKY, New York.

CHARACTERISTIC ALTERATIONS IN GANGLION CELLS IN CASES OF HEPATOLENTICULAR DEGENERATION AND OTHER HEPATOCEREBRAL DISEASES. N. W. KONOWALOW, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **171**:229 (Feb.) 1941.

Konowalow previously described (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **169**:220, 1940) alterations in astrocytes which account for the Alzheimer glia cells associated with pseudosclerosis. He now describes similar changes in the ganglion cells, which he observed to be extensive in 3 of 8 cases of hepatolenticular degeneration. The cell changes were encountered especially in the large cells of the striatum, in the medial and central nuclei of the thalamus, in the pontile nuclei and in the deeper layers of the cerebral cortex. The cell nucleus was enlarged to about twice its size, while the protoplasm was broken down and showed chromatolysis. In some cells the nuclei seemed inordinately large because of the breakdown of the cell body, but in most there was actual enlargement of the nucleus. Another, less frequent, change in the ganglion cells was the disappearance of the chromatin in the nucleus, with relative intactness of the cytoplasm.

SAVITSKY, New York.

LIPOMA OF CORPUS CALLOSUM. HORST MERKEL, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **171**:269 (Feb.) 1941.

Merkel reports the case of a woman of 57 who died of pemphigus. There were no mental or nervous symptoms during life. Necropsy revealed widespread pemphigus, bronchopneumonia, lipomatosis and a lipoma lying on the left side of the corpus callosum. This tumor could be followed from the rostrum to the region of the splenium, around which it wound itself. It was then observed to be connected with a yellow-white mass of fat tissue in the choroid plexus. The lipoma was 7 mm. wide anteriorly and 6 mm. wide posteriorly. It was distinct from the surrounding brain tissue. There was also some fatty tissue in the region of the chiasm.

Microscopic examination showed, in addition to fat cells, a considerable amount of collagenous tissue. This connective tissue extended even into the corpus callosum, especially its posterior portion. A few fat cells were also seen within the tissue of the corpus callosum. There was no developmental defect of the callosum itself.

The author agrees with Krainer, who maintained that lipomas of the corpus callosum are due to developmental defects. Some of the embryonic meningeal tissue fails to differentiate. The presence of this tumor tissue in the corpus callosum is in support of the hypothesis that the corpus callosum is formed by the fusion of structures coming from both cerebral hemispheres.

Twenty-four other cases of lipoma in the region of the corpus callosum were collected, in only 7 of which there were no definite developmental defects of the corpus callosum.

SAVITSKY, New York.

Psychiatry and Psychopathology

A STUDY OF FRONTAL LOBOTOMY: NEUROSURGICAL AND PSYCHIATRIC FEATURES AND RESULTS IN 22 CASES WITH A DETAILED REPORT ON 5 CHRONIC SCHIZOPHRENICS. EDWARD A. STRECKER, HAROLD D. PALMER and FRANCIS C. GRANT, *Am. J. Psychiat.* 98:524 (Jan.) 1942.

Strecker, Palmer and Grant report the results of frontal lobotomy on psychotic patients. It is their opinion that this drastic procedure should be used only as a last resort. They conclude that a year should elapse after operation before one makes even a preliminary judgment as to the result. Twenty-two patients were studied, including 16 with agitated depression, 5 with schizophrenia and 1 with a sex problem. There were 2 operative deaths, 1 as the result of anesthesia and the other from postoperative hemorrhage. Both deaths occurred in the group with agitated depressions. Twelve of the 16 patients comprising this group were sufficiently recovered to leave the institution, and only 1 failed to show some improvement. Palmer notes that patients with agitated depressions showed not only diminution in agitation and loss of the affective disturbance but unwillingness to review the thought content present during the psychosis. Two of the 5 schizophrenic patients were sufficiently recovered to leave the institution; the other 3 were improved. Strecker points out that complete recovery must not be expected in the stormy, violent, destructive, aggressive type of schizophrenia such as characterized the group in this study. The postoperative reeducation and rehabilitation of patients are considered to be of the utmost importance.

FORSTER, Boston.

A MODIFIED RORSCHACH TECHNIQUE FOR THE DESCRIPTION OF TRANSITORY POST-CONVULSIVE PERSONALITY STATES. EDWARD J. STAINBROOK, *Rorschach Research Exchange* 5:192 (Oct.) 1941.

Because controlled convulsion conditions make possible a closer investigation of personality reintegration after a severe convulsive crisis, psychiatric utilization of therapeutic convulsions has increased greatly.

In order to obtain a "cross section" description of the personality at various times during the recovery process, a modification of the Rorschach test has been devised. This modified test makes it possible to obtain a Rorschach psychogram of personality reactions as early as five minutes after a convulsion. In this modified test the patient is subjected to cards I, II and III as soon as he is able to respond, and then is presented with these same cards in the same order throughout the following hour. On the next day of treatment the same procedure is followed with cards IV, V and VI. On the following treatment day cards VII, VIII, IX and X are presented in the same fashion. In this way responses to all cards are assembled into composite Rorschach records for each five minute period after the convulsion. During the immediate postconvulsive half-hour, when the

responses generally show the greatest change, the maximal number of "cross sectional" profiles can be obtained.

In studying Rorschach reactions after subconvulsive electric shock and in a few cases of major convulsions, cards III, V and X were used—card III for its frequent evocation of movement responses, card V for its popular form frequency and its compact unitary form and card X for its color and detail. A similar study is being made with Klopfer's technic of "testing the limits" as an additional means of obtaining a description of postconvulsive reactions.

MARCOVITZ, Philadelphia.

A SURVEY OF THE RESULTS OF INTELLIGENCE TESTS IN PSYCHOSIS. M. B. BRODY, *Brit. J. M. Psychol.* **19**:215, 1942.

Brody reviews in detail reports of results of mental tests in cases of the psychoses, with almost exclusive emphasis on intelligence tests and those of cognitive functions. To aid in the evaluation of these results, he first summarized the recent observations on the normal changes in mental ability after early maturity. Ability in vocabulary tests and closely related tests, such as defining abstract words, remains stationary or increases in later life. Decline is apparent in the responses to most other tests, particularly after the fifth decade.

In cases of psychoses mental tests show that vocabulary ability is best maintained, verbal ability next, while nonverbal test ability is severely impaired. The vocabulary rating can be a measure of the patient's initial ability. It is important, since like patterns can result from different causes, to interpret each test record separately and individually, carefully evaluating the extent of the failure against the normal failure for that age and analyzing the degree of cooperation which may be interfered with by invalidating disorders of mood or stream of mental activity.

Brody believes a genuine decline in ability or dementia occurs with organic psychoses. The same pattern of failure in biogenic psychoses is more often due, however, to "pseudodementia," i. e., to disorders of mood, etc.; the mental level is quantitatively intact, while its function is interfered with.

The qualitative aspects of mental test performance are described in some detail. Some of the observations include inertia of functioning, weakness in the directional control of thought, impairment of "planfulness" and, in schizophrenia, a childlike associative type of thought, with the special qualities of asyndesis, metonymic distortion and interpenetration.

He describes the use of mental tests by some workers for prognosticating the value of shock therapy or for testing its results.

ALLEN, Philadelphia.

HYPERTHYROTIC CATATONIA: A SCHIZOPHRENIC SYMPTOM-COMPLEX. R. E. HEMPHILL, *J. Ment. Sc.* **88**:1, 1942.

Hemphill studied the distribution of goiter among 4,750 patients with mental disease. No patient with early schizophrenia had a nontoxic goiter. Hyperthyroidism was found to be rare in schizophrenic persons, but when it occurred it was always associated with a particular form of reaction, characterized by "a period of varying schizophrenic symptoms with auditory hallucinations, an acute episode when visual hallucinations appear, with distortion of the body-image, inability to differentiate clearly parts of the body and other evidences of instability of the boundaries of the ego. This phase is succeeded by catatonic stupor. In severe cases the end result is dementia, in others towards recovery with repetition of the cycle."

Hemphill compares this "hyperthyrotic catatonia" to the periodic catatonia described by Gjessing and concludes that there are types of schizophrenia which appear to be derived from special endocrine disorders. Systematic determination of every assayable hormone early in these illnesses may provide a clue to their cause.

DRAYER, Philadelphia.

THE PROGNOSTIC FACTORS OF ADOLESCENT PSYCHOSES. A. BARHAM CARTER, J. Ment. Sc. 88:31, 1942.

Carter studied 78 cases of adolescent psychosis. Favorable factors seemed to be some soundness of stock, often associated with a pyknomorphic physique; a helpful environment; severe, acute psychotic episodes, and preservation during the psychosis of "normal," though possibly exaggerated, emotional reactions. On the other hand, an insidious onset, dissociation of emotional reaction, increasing withdrawal from the environment and persistence of symptoms were all indications of a poor prognosis. Particularly unfavorable symptoms were chronic catatonia, stereotypy and grotesque behavior.

DRAYER, Philadelphia.

ELECTRO-ENCEPHALOGRAPHY IN CASES OF MENTAL DISORDER. W. GREY WALTER, J. Ment. Sc. 88:110, 1942.

Walter reports the results of electroencephalographic studies on 72 patients with various types of mental disorder. The records of patients with epilepsy, cerebral atrophy, organic cerebral lesion and catatonic schizophrenia showed definite abnormalities. Patients with other types of schizophrenia and the affective psychoses had records within normal limits. The author concludes that the electroencephalogram may be helpful in discriminating between organic and purely mental disorders. He suggests that the unusual features in the records of persons with a catatonic schizophrenia may reflect abnormalities in the electrical resistance of the tissues superficial to the brain.

DRAYER, Philadelphia.

THE INVESTIGATION OF PERSONALITY IN PATIENTS TREATED BY PREFRONTAL LEUCOTOMY. E. L. HUTTON, J. Ment. Sc. 88:275, 1942.

In this preliminary report, Hutton suggests that in those mental disorders apparently benefited by prefrontal leukotomy (melancholia, anxiety states, obsessional and compulsive neuroses and schizophrenia) "the patient fails to attend to the real world around him, his attention being devoted almost exclusively to the autistic maintenance of those ideas and images out of which he creates the illusory world in which he lives, his actions being determined in accordance with his fantastic beliefs and not with the demands of reality." After leukotomy such autistic thinking is interrupted, and the patient responds directly to stimuli from the real environment. Associative memory, based on long-established patterns of behavior and thinking, seems to be relatively undisturbed by the operation. Hence, as long as such patients do not have to initiate the thinking, and are responding only to the thoughts of others, they appear to be as "intelligent" as they were prior to their illness.

DRAYER, Philadelphia.

PSYCHIATRIC SYNDROMES FOLLOWING BLAST. E. W. ANDERSON, J. Ment. Sc. 88:328, 1942.

Anderson discusses the problems involved in determining what may rightly be considered the effects of blast. Especially difficult to obtain are accurate accounts of the incident. In only 2 of the 8 cases described was it reasonably certain that there had been no associated head injury of the ordinary type. The fatigue and excitement attendant on combat situations, as well as the absence of trained observers in most instances, prevent accurate study of the immediate reactions to high explosives. Lest transitory evidences of organic damage become obscured and lost, early reference of such patients to a competent psychiatrist is recommended.

Forgetfulness, difficulty in concentration and general slowing down of motor functions were found to be characteristic of this series. Affective lability for a time after the explosion was described by some patients, but apathy was a more common reaction. A fortnight's rest in bed with proper sedation is regarded as the best treatment.

The author proposes that in legal action, because of the present incompleteness of knowledge, an amnesic patient who has been exposed to a blast should be given the benefit of whatever doubt may exist as to an organic basis for his defect.

DRAYER, Philadelphia.

DRUGS AND MENTAL DISEASE. MERRILL MOORE, ALICE F. RAYMOND and M. G. GRAY, *Confinia neurol.* 4:238, 1942.

Of 115,845 admissions to the mental disease hospitals of Massachusetts during the period between 1917 and 1937, there were 841 cases of mental illness associated with the excessive use of drugs. The conditions in these cases were diagnosed either as "psychosis due to drugs and other exogenous toxins" or as "drug addiction without psychosis." Thus, the admissions due to drugs and chemical agents represent an average of 0.7 per cent of all admissions during the period reviewed. In the 841 cases of mental illness associated with drugs and chemical agents, the order of frequency of the agent was as follows: opium derivatives, 363 cases; barbiturates, 208 cases; bromides, 101 cases; others sedatives, 27 cases; analgesics, 15 cases; gases, 19 cases; metals, 18 cases. There were 54 cases of addiction to miscellaneous and unidentified substances, and in 36 cases the disease was not verified as due to drugs or chemical substances.

The authors noted a higher incidence in the group of persons with college educations and those coming from the marginal economic level than among the general group of patients admitted to mental disease hospitals. A larger percentage of these patients were native-born residents, and there were more naturalized persons than aliens. There was a higher percentage of unmarried persons in the group studied than in the general population of the state or in the total number of patients admitted to the Massachusetts mental disease hospitals. The recovery rate for patients with mental disease due to drugs is high and the death rate low. The immediate prognosis of mental illness due to drugs is more favorable than that for other types of acute mental disorders. It is not possible to determine from these data whether mental disease due to drugs is increasing or decreasing.

DEJONG, Ann Arbor, Mich.

Cerebrospinal Fluid

THE GROUP OF DEMENTIA PRAECOX PATIENTS WITH AN INCREASE OF THE PROTEIN CONTENT OF THE CEREBROSPINAL FLUID. WALTER L. BRUETSCH, MAX A. BAHR, JOSEPH S. SKOBBA and WILLIAM J. DIETER, *J. Nerv. & Ment. Dis.* 95:669 (June) 1942.

The authors studied the spinal fluid of 1,281 of patients with dementia praecox. Quantitative protein determinations, Pandy and Ross-Jones tests, cell counts and colloidal gold and Wassermann tests were performed. Among 634 newly admitted patients, the protein content of the spinal fluid was above 45 mg. per hundred cubic centimeters in 15 (4.4 per cent) and in 8 females (2.7 per cent). Among the old patients there was an increased protein content of the spinal fluid in 5.9 per cent of the males and 3.7 per cent of the females. None of the patients had a positive serologic reaction. There was little variation in the protein content in those cases in which repunctures were made at intervals. No clinical features were characteristic of the patients with increased spinal fluid protein. The authors speculate on the possible relationship of the cases with an increased protein content to cases of acquired cerebral syphilis of the meningovascular type and to cases of congenital syphilis, since it is known that the only observable abnormality of the spinal fluid in such cases may be a slightly increased protein content of the spinal fluid. Stigmas of congenital syphilis were not found, although a recapitulation of anamnestic data indicated that in a few cases a history suggestive of parental syphilis was present. One patient with a protein content of 130 mg. per hundred cubic centimeters died four months after admission, during a period of catatonic

excitement. Necropsy observations were within normal limits except for a few meningeal areas, where a slight cellular proliferation was observed. The authors conclude that in most cases the abnormal changes in the spinal fluid could not be explained.

CHODOFF, Langley Field, Va.

LUMBAR AND CISTERNAL SPINAL FLUID: NORMAL VARIATION. ANDRÉ TEIXEIRA LIMA, FRANCISCO TANCREDI and JOÃO BAPTISTA DOS REIS, Arq. serv. assist. psicopat. do Estado de São Paulo 5:391 (Sept.-Dec.) 1940.

Specimens of spinal and of cisternal fluid were removed from 71 patients in a mental disease hospital, none of whom had positive neurologic signs. Twelve cubic centimeters were removed by the cisternal and lumbar routes. The total protein content of the cisternal fluid varied from 0.10 to 0.26 Gm. per hundred cubic centimeters and that of the lumbar fluid from 0.12 to 0.44 Gm. The lumbar fluid contained more protein than the cisternal fluid in 54 cases; the amounts were equal in 7 cases, and the cisternal fluid contained more in 8 cases. The authors consider the normal number of cells in the fluid to be 0 to 3 cells per cubic millimeter. There is a tendency for more cells to be present in the lumbar fluid. The ratio between the amount of protein in the lumbar and that in the cisternal fluid was 1 or more, but never over 3.

SAVITSKY, New York.

CREATININE CONTENT OF CEREBROSPINAL FLUID. JOÃO BAPTISTA DOS REIS, HANS SCHMIDT and ALAN LARA WILLIAMS, Arq. Serv. assist. psicopat. estad. São Paulo 6:243 (Sept.-Dec.) 1941.

The authors used the Pulfrich (photometric) modification of the Folin method in studying the creatinine content of the spinal fluid. It was found that the presence of protein did not in any way affect the determination of creatinine. The amount of creatinine in the cisternal fluid of 100 patients in a mental disease hospital who had no organic disease varied from 0.87 to 1.48 mg. per hundred cubic centimeters. In most cases (32) 1.06 to 1.14 mg. was noted. In 50 cases simultaneous determinations of creatinine were made on the blood and on the spinal fluid. The ratio of creatinine in the spinal fluid to that in the blood was always less than 1. The values for the spinal fluid varied from 47 to 96 per cent of the creatinine in the blood and in most cases from 70 to 80 per cent. In 10 cases simultaneous lumbar and occipital punctures were made, and the amounts of creatinine in the two types of fluid were compared. The creatinine content of the lumbar spinal fluid in 9 cases was less than that of the cisternal fluid. In 1 case the level of creatinine in the cisternal and that in the lumbar fluid were the same.

SAVITSKY, New York.

Muscular System

POTASSIUM AND MUSCULAR DISORDERS. J. N. CUMINGS, J. Neurol. & Psychiat. 4:226 (July-Oct.) 1941.

Cumings found no abnormality in the potassium content of muscles or any therapeutic effect of prostigmine in the majority of muscle diseases and in conditions in which fat or fibrous tissue replacement of muscle occurs. However, in a patient with a parathyroid tumor there seemed to be an association between the muscular weakness and the low potassium level in the muscles. Two patients with severe myasthenia gravis, who were receiving a diet resulting in a positive potassium balance, were studied. As in previous experiments, injections of prostigmine methylsulfate liberated potassium from muscles, resulting in an increase of potassium in the serum. In addition, the author found that red blood cells also showed an increase in potassium content. Therefore, the increase in the total potassium content of the blood accounted better for the liberated muscle potassium than the serum alone. There was no increase of potassium in the urine after injection of prostigmine. Division of motor nerves to muscles in patients, as well

as in experiments with animals, did not affect the potassium content of the muscles. Cumings concludes that an abnormality in potassium content of muscles is primarily associated with myasthenia, although it may not actually cause the disease. The author was unable to produce muscular disorders in rabbits with substances extracted from the roots of American and Chinese varieties of yellow jasmine.

MALAMUD, Ann Arbor, Mich.

THE EFFECT OF PROSTIGMIN ON THE URINARY EXCRETION OF POTASSIUM IN THE NORMAL SUBJECT. J. N. CUMINGS, *J. Neurol. & Psychiat.* 4:235 (July-Oct.) 1941.

In cases of myasthenia gravis, injections of prostigmine methylsulfate liberate potassium from the muscles into the blood, but the urine shows no increase in the amount of potassium. Studies on 3 normal subjects showed that injection of prostigmine had no effect on the excretion of potassium in the urine. This offers further proof that prostigmine is not the direct cause of the retention of potassium in patients with myasthenia.

MALAMUD, Ann Arbor, Mich.

THE FREQUENCY, ETIOLOGY AND PROGNOSIS OF EYE MUSCLE PALSIES. E. KESSLER, *Confinia neurol.* 4:159, 1942.

Kessler has prepared a statistical study of the frequency, etiology and prognosis of palsies of the ocular muscles, basing her conclusions on 233 cases. Paralysis of the internal branch of the oculomotor nerve and of the levator palpebrae superioris and paralysis of associated movements were excluded. The abducens nerve was most frequently involved, followed by the external branches of the oculomotor nerve and then by the trochlear nerve. Ocular palsies were observed twice as frequently in men as in women. Etiologic factors were listed in the following order: fracture of the skull, apoplexy, congenital paralysis, trauma to the orbit, multiple sclerosis, brain tumor and syphilis. Ocular palsies were observed most frequently from the third to the sixth decade. The prognosis of ocular palsies following fracture of the skull or apoplexy is relatively good; more than half of all the patients recovered or showed improvement. DEJONG, Ann Arbor, Mich.

Congenital Anomalies

COMBINATION OF FRIEDREICH'S ATAXIA AND CHARCOT-MARIE-TOOTH ATROPHY IN EACH OF TWO BROTHERS. ALEXANDER T. ROSS, *J. Nerv. & Ment. Dis.* 95:680 (June) 1942.

Ross points out the rather close relationship existing in certain cases between Friedreich's ataxia and peroneal muscular atrophy of the Charcot-Marie-Tooth type. Cases partaking of the characteristics of both these syndromes have been described by many investigators. Ross reports the cases of 2 brothers presenting a combination of these two conditions. A sister had undoubted Friedreich's ataxia, and a maternal cousin was a high grade moron with signs of mild involvement of the pyramidal tract and "Friedreich feet." One of the brothers reported was a moron with slurred speech, bilateral weakness of the external rectus muscles, nystagmus, bilateral cerebellar signs, weakness and pronounced atrophy of the peripheral musculature of the extremities, absence of deep reflexes and diminution to loss of all modalities of sensation in a glove and stocking distribution. Examination of the other brother gave similar results, with a more pronounced degree of mental defect.

The observations on this family lend support to the belief that the neurologic hereditary degenerative diseases represent abiotrophies of certain parts of the nervous system, which in individual cases may manifest themselves in isolated, abortive or bizarre combinations. The relation of these cases to the syndrome of Roussy and Lévy and to the familial spastic paraplegias is discussed.

CHODOFF, Langley Field, Va.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

ABRAHAM A. BRILL, M.D., *President, New York Neurological Society, Presiding Joint Meeting, May 5, 1942*

The Electroencephalogram in Epilepsy. DR. FRANCIS A. ECHLIN.

The present work is based on an electroencephalographic and clinical study of 100 cases of epilepsy.

The merits of the Gibbs-Lennox (ARCH. NEUROL. & PSYCHIAT. 39:298 [Feb.] 1938) and the Jasper-Kershman electroencephalographic classification of the epilepsies are discussed.

The work to be presented is based on the Jasper-Kershman classification (ARCH. NEUROL. & PSYCHIAT. 45:903 [June] 1941), which was found to be the most satisfactory for the routine study of epileptic patients, especially since most patients must be studied between seizures.

Technic.—A four channel, ink-writing electroencephalograph apparatus, built by Rahm, was used throughout the study. Electrode placements were the same as those described by Jasper, Kershman and Elvidge (ARCH. NEUROL. & PSYCHIAT. 44:328 [Aug.] 1940). One hundred and ninety electroencephalograms taken from the 100 patients were studied. The work was done in the neurologic and neurosurgical service of Lenox Hill Hospital.

Summary of Results.—The characteristic feature of the records was the recurrent or paroxysmal appearance of high voltage waves, a phenomenon which Jasper and Kershman called paroxysmal hypersynchrony (exemplified in the first two groups to be described later). Most of these discharges occurred at frequencies which may be regarded as abnormal, and therefore, in addition to hypersynchrony, there was usually dysrhythmia, as described by Gibbs, Gibbs and Lennox (*Brain* 60:377, 1937).

In attempting to classify the records, I, like Jasper and Kershman, found that this could best be done on the basis of localization studies, and cases were grouped according to the site of the abnormal discharges in the brain. The different wave forms and patterns were of considerable help in the analysis of individual cases, but were of secondary importance, especially in cases in which a focal abnormality was present.

Analysis of the electroencephalographic records without reference to other data revealed that they could be divided, according to the Jasper-Kershman classification, with a considerable degree of accuracy into four groups.

Localized unilateral cortical abnormality (30 cases). The wave forms and patterns encountered were: random spikes, 2 cases; random sharp waves, 24 cases; random delta waves, 4 cases, and paroxysmal rhythmic discharges, 5 cases, the last being also included under sharp wave forms. It should be noted that these so-called localized discharges may at times cover a large area of one hemisphere.

Bilaterally synchronous abnormality from homologous areas in the two hemispheres (35 cases). The wave forms and patterns present were: 3 per second wave and spike patterns, 7 cases; sharp waves, 14 cases; 3 per second waves, 13 cases, and 6 per second waves, 5 cases, 4 of which were placed in the sharp wave group as well:

We agree that the 3 per second wave and spike pattern and the 3 per second wave form seem to originate from a deep midline pacemaker. The sharp wave discharges appear at times to arise deep in one temporal lobe and to be transmitted as a "mirror" focus to the opposite hemisphere.

Diffuse, nonlocalized abnormality (15 cases). This type of abnormality was characterized by disorganization of the alpha rhythm, variation in amplitude and frequency of the cortical rhythms, but without hypersynchrony (as in the first two groups), and scattered delta activity of low amplitude. These observations differ from those of Jasper and Kershman.

Normal electroencephalograms (20 cases). It was at times difficult to distinguish between a record showing a slight diffuse abnormality and a normal electroencephalogram.

Illustrations of the various types of abnormality are shown. A combined analysis of the clinical data and the electroencephalograms is now presented.

Localized unilateral cortical abnormality (30 cases). In 70 per cent of the cases in which this type of electroencephalogram occurred there was a clinical history of focal epilepsy; that is, the pattern of the attacks suggested a focal cortical origin similar to that indicated in the electroencephalogram. In 53 per cent of these cases the presence of a pathologic lesion was proved by air studies, operation or postmortem examination of the region of the cortex indicated in the electroencephalogram. An analysis of the different types of clinical seizures and their relation to wave forms and patterns is presented. Attacks of the petit mal variant and the psychomotor type were not uncommon.

Bilaterally synchronous abnormality (35 cases). In 92 per cent of these cases generalized grand mal seizures were present without any clinical pattern to suggest an origin in a focal area of the cortex. The initial symptom was usually loss of consciousness, which was in keeping with an origin in a deep midline area or sudden involvement of the greater portion of the cortex of both hemispheres. In 35 per cent of the cases petit mal attacks and in 38 per cent seizures of the petit mal variant or the psychomotor type occurred. The relation of the clinical attacks to the wave forms and patterns is discussed. Seizures of the petit mal variant and the psychomotor type were most common in those cases in which bilaterally synchronous sharp waves arose from the temporal lobes. In cases of a 3 per second wave and spike or a 3 per second wave pattern (20 cases) the average age at onset of seizures was 12 years, and the average age at the time of examination was 18 years.

Slight diffuse abnormality or normal electroencephalograms (35 cases). In 92 per cent of cases grand mal seizures without clinical localizing features were present. In 17 per cent there were petit mal attacks. In 20 per cent attacks of petit mal variant or psychomotor type occurred. In 14 per cent the clinical history suggested focal cortical onset. The site of origin of the seizures in these cases was hard to determine because of the relative inactivity of the abnormal focus. The average age at onset of the attacks in this group was 26 years and the average age at the time of study was 37 years. The fact that the epileptic focus in these cases was relatively inactive electrically may be related to the age of the patients, for Golla, Graham and Walter (*J. Ment. Sc.* 83:137, 1937), in a study of 214 epileptic patients, found few abnormal electroencephalograms in persons over 40 years of age.

A classification of the electroencephalograms based on the pattern of the clinical seizure is also shown.

In summary, it may be stated that the pattern of clinical seizure shows a close relation to the form of the electroencephalogram, especially with regard to localization. The observations of Jasper and Kershman have been largely corroborated.

DISCUSSION

DR. PAUL HOEFER: I should like to say a few words about the clinical usefulness of the records of brain waves. My associates and I still use the Gibbs and Lennox classification, which, even if it may turn out to be only a working

hypothesis, has helped us a great deal, just because it is an attempt to correlate the clinical and the electrical features. It is still possible for me, at least, to use this correlation, with slight modifications.

It is significant that during clinical seizures we obtain the specific electroencephalographic patterns, except perhaps in grand mal attacks, when we see spike and wave groups in addition to the high voltage, rapid activity.

Between petit mal seizures, or perhaps I should say in the absence of clinically noticeable petit mal seizures, we find the synchronous 3 per second spike and wave pattern in about 85 per cent of our cases.

Between grand mal seizures, however, and during psychomotor seizures we obtain the specific seizure pattern in only 55 to 60 per cent of our cases, and in an additional 20 per cent of the cases we find patterns attributed to another form of seizures, such as the grand mal pattern in cases of psychomotor epilepsy and vice versa. In another, smaller group of cases of grand mal seizures we find only a spike and wave pattern, as does Dr. Echlin.

There are several possible explanations for this; it may be that in these cases there are actually brief clinical or subclinical attacks of both forms of the disease, though only the more dramatic of the two is detected clinically. It is also possible that the brain wave patterns are not as specific as was thought at one time.

As to the focal origin of the generalized seizures, we have not had the experience of the Montreal group. We have found these foci shifting, and I know of cases in which after operation a focus has appeared in another part of the brain. Only in clinically strictly focal motor seizures have we found a good correlation with the brain wave record.

However, only now are the meaning of the brain waves and their relation to action potentials of brain cells and fiber tracts beginning to be understood. Electroencephalography, I believe, is the method by which the problem should be studied, and clinical interest, no matter to what school of thought one belongs, is the best stimulus to continuation of this work.

DR. MARGARET RHEINBERGER (by invitation): Perhaps the reason for my preference for Dr. Echlin's point of view lies in the fact that I have found the general clinician to be imbued with the idea that electroencephalography can tell him whether a patient has "epilepsy," by which he means what I should call functional epilepsy. I try to impress on any clinician with whom I come into contact the preferability of his avoiding the use of the clinical term with reference to the electrical patterns which are obtained. Dr. Echlin's figures, based on a study of 100 patients who had epilepsy, showed 20 per cent with normal electroencephalograms. I think my co-workers and I have about the same percentage in our records, which comprise tracings for approximately 350 epileptic patients out of a much larger group of persons with other disorders as well. About 30 per cent of all the patients who had clinical epileptic attacks and who came to our laboratory for investigation had tumor.

I should like to emphasize the point that although paroxysmal hypersynchrony is characteristic of the majority of cases of epilepsy, as Dr. Echlin has pointed out, and as I am sure Dr. Hoefler will agree, there are instances in which the clinical focus of an epileptic attack is represented electrically not by hypersynchrony but by depression of amplitude, a loss or slight slowing of the normal rhythm. Such changes have not, so far, been considered in discussions on electrical patterns associated with epilepsy, and yet they cannot be ignored as indications of localized disturbance.

A case which is of interest from the point of view of localization not only of epileptic patterns but of cerebral abnormalities in general is that of a woman who came to the hospital with which I am associated with a high grade of papilledema and with no clinical neurologic localizing signs. Her electroencephalographic pattern was confusing in that from the right frontal area there was a slow wave, more or less paroxysmal discharge, not of high amplitude, while the left parietal region showed slowing of the rhythm which did not appear to be correlated with the paroxysmal discharge recorded from the frontal area. On the basis of the

electric pattern we felt we were incapable of making a decision as to which of these two changes was of greater importance. Just prior to the taking of the electrical record the patient had her first and only seizure, which involved only the left side of the body, and it was therefore assumed that the electrical change from the right frontal area was correlated with the damage which had produced the seizure. Because of this observation and the fact that whatever other clinical evidence there was pointed to the same area of localization, it was decided that she had a tumor of the right frontal region. She did not. The tumor was in the left parietal lobe, and the reason for the seizure, which was left sided, and the electrical discharge from the right frontal region was a recent hemorrhage in that area. The tumor was a meningioma, and if we had known a little more than we did we might have saved the patient's life.

Psychopathologic Review of Senile and Arteriosclerotic Disorders. DR. OSKAR DIETHELM (by invitation).

It is generally accepted that memory disorders and senile personality changes, decline of judgment, disorders of comprehension and attention, disorientation and apathy form the psychopathologic reaction in senile and arteriosclerotic psychoses. With the aid of a group of psychologic tests, patients with such disorders were studied. An especially planned maze test permitted the study of orientation to a task and of memory. Persons with senile disturbances showed difficulty in orientation to a task and in learning, diminished retention and recall, shortened span of active attention, tendency to perseveration and use of grooves of thinking.

Anxiety shortens the span of active attention and diminishes retention and relearning. The presence of anxiety in senile or arteriosclerotic patients increases disorders of retention and attention and difficulty in understanding a task. Thinking disorders become especially pronounced through the presence of depressive thinking and may lead to a confusional disorder.

Minor physical ailments, found especially with arteriosclerosis (kidney and cardiovascular disease), minor infections, dietary disorders and avitaminosis, may also cause disturbances of thinking and memory, which in the past have been explained by cortical damage. The outlook in many cases of so-called deterioration may be favorable if physical treatment can eliminate these complications and psychotherapy can alleviate anxiety.

DISCUSSION

DR. LAWRENCE S. KUBIE: There is great difficulty in isolating the machine factor in intellectual performance from the emotional element. This is evidenced in the difficulty of testing the thinking capacity apart from the influence of the emotional background. All have encountered this problem in examining old people and have found it extremely hard to decide whether a reduction in the output of the thinking machine was due to a defect in the machine itself or to the accompanying depression or anxiety or to a combination of the two. Dr. Diethelm condensed his presentation so much that it was not clear to me how the maze test makes it possible to differentiate between the play of emotional factors and a reduction in the intrinsic efficiency of the machine itself. I wonder whether electroencephalography, when correlated with these studies, throws any light on this problem. I recall the theory that used to be advanced to differentiate between the arteriosclerotic and the senile disorders and the emphasis that Hoch laid on what he called a "mental tension" defect. By this he meant not an isolated mental function but a complex product of intellectual and emotional activities. He felt that in the arteriosclerotic patient this loss in "mental tension" was primary and that such a patient was aware of his difficulty and suffered acutely because of it. I should be interested to know whether Dr. Diethelm's studies have borne this out.

DR. OSKAR DIETHELM: Dr. Kubie embarrassed me slightly when he asked about the maze test; because of the limited time for the presentation I merely mentioned that it was an essential test, but there are many others.

In cases in which my associates and I took electroencephalograms we were never able to see any clear correlation with the results of these tests.

I do not know enough about Hoch's concept of "mental tension" to discuss it. I never saw it mentioned in the literature, but from Dr. Kubie's description I think it corresponds to what one finds in some senile patients. Mental tension is hard to define, and I have never felt that Bleuler was able to define it well, either.

Cachexia of Mental Origin: Nature and Management. DR. JOHN L. SMALLDON (by invitation).

This paper constitutes a summary of a study of 6 girls at the New York Hospital, Westchester Division, whose illnesses were initiated by self starvation and the consequent development of a cachectic state. Significant similarities characterize the 6 cases. The psychopathology is stressed. Each case presents the well known history and physical signs of anorexia nervosa, but all have been considered by a number of examiners, who have observed the patients daily for months or years, to be cases of dementia praecox rather than of compulsive-obsessive neurosis. It is speculated that in some cases of compulsive-obsessive neurosis characterized by anorexia nervosa the condition will on later observation be found to have progressed beyond the realms of a psychoneurosis into a psychosis. For this reason, in addition to the fact that the term anorexia is inaccurate in describing this voluntary self starvation, it is suggested that the condition be labeled "cachexia of mental origin," rather than anorexia nervosa.

DISCUSSION

DR. LELAND E. HINSIE: The following mental factors are common to all patients: mentally induced emaciation; fear of enlargement through eating; fear of effeminacy; absence of overt sexuality; fixation at an oral and anal level, with predominance of anal trends, evidenced by excessive cleanliness or the opposite (smearing of feces), orderliness, stubbornness, hoarding and guilt over eating (oral impregnation; sexual excitation caused by intake of food); reversal of sexual role in parents, and energy prevented from entering the sexual zone and kept at anal and oral levels. The psychopathologic state was essentially preoedipean.

The physical factors common to all patients were female sex, early maturity, asthenic habitus; inadequate development of sex organs; masculine distribution of hair, and pronounced disturbances in the vegetative nervous system.

Diagnosis.—Authorities differ on nosologic classifications. Evidence favors the diagnosis of a form of psychoneurosis. Personally, I believe a reaction of this type is best understood as a compulsive-obsessive psychoneurosis, the psychopathologic basis of which is fixation of energy on oral and anal factors. I believe, also, that somatopathologic factors play an equally important role. Insight into the illness (not the nature of it) is fully retained. The projection mechanism is usually absent, and, when present, it constitutes but a small part of the total difficulty. The patients are introverted in that their attention is riveted on their physique, but they appear not to be schizoid, for they are not averse to socialization. A psychoneurotic person, asocialized because of phobias or anxieties, is not said to be schizoid. A depressed patient (of the manic-depressive type) is not said to be schizoid, though object cathexis is scanty.

The physique may be called on, so to speak, to bear the brunt of any kind of mental conflict. For example, the patient with schizophrenia of the hebephrenic or catatonic form may, and often does, put all of his primitive mentality in terms of physical functions. The language of such schizophrenic patients is a body language that speaks from the phylogenic level. The neurasthenic patient speaks from the ontogenic level, particularly from the levels of orality and anality. Mental cachexia, I believe, is closely allied to neurasthenia, which is, in turn, closely related to the compulsive-obsessive syndrome. Patients with conversion hysteria, likewise, use their physique to express a mental conflict. In these

instances the conflict issues from the genital level. I believe it would better fit current concepts to enter anorexia nervosa as a subdivision of the psychoneuroses.

Thus far there is no specific form of therapy known to influence this condition favorably.

DR. A. A. BRILL: In listening to Dr. Smalldon, and particularly to Dr. Hinsie, who emphasized that these patients direct all their energy to the oral and anal openings, it occurred to me that instead of calling the condition "mental cachexia," which in my opinion is not a description, it would be best to designate it as "gastruloid regression." I refer to Haeckel's theory of the gastraea, which consists of the outer layer, from which the skin and the nervous system develop, and the inner layer, which forms the alimentary canal and the other organs. According to Haeckel, all metazoa start as gastrulae, i. e., as beings resembling a plum with an upper and a lower gateway. As the patients described by Dr. Smalldon and others center everything on the mouth and the anus, we may look on them as phyletic reversions to the gastrula.

DR. IRVING H. PARDEE: I became interested in this syndrome because it simulates Simmonds' disease, the syndrome of pituitary cachexia. I have worked with a large number of patients with this disorder, about 20 altogether, and I should like to aline myself with Dr. Hinsie and consider the disease as a psychoneurosis. I have not seen any patients with the advanced form, such as Dr. Smalldon described. Most of the patients I have seen have been ambulatory, usually either living at home or able to go to a general hospital or the Neurological Institute for treatment. It may be that some of them are schizophrenic, but those I have seen were not.

I should like to bring out two points from the physical side. First, I do not think the amenorrhea belongs in the field of psychopathology. I believe it is the result of starvation and hormone deficiency. A friend who lives in Puerto Rico told me that when they have a period of starvation down there amenorrhea is common among women. Therefore I am not willing to subscribe to the theory that this disturbance is due to fantasies or any such psychological factor.

Dr. Hinsie brought up the other point, that of hair growth. It is reported that in the Irish potato famine of 1858 the women were noted to grow hair on the face and body as part of the starvation situation. There is no evidence of deficiency of the pituitary, thyroid, gonads or adrenals. Excessive hair growth is usually the result of a hyperplastic disturbance of the pituitary or the adrenal glands. In this syndrome there is a deficiency of these glands, rather than otherwise, and it is a functional deficiency, secondary to starvation. No actual atrophy is present in these glands. One patient had her appendix removed in the course of her illness, and I prevailed on the surgeon to take out a portion of the ovary for examination. The tissue was normal, with normal follicles, and though she had amenorrhea, all the setup for good ovarian function was present.

I look with fear on the use of insulin in treatment of these patients. I know Dr. Smalldon used it with a number. The patients we studied carefully have all shown uniformly low blood sugar curves, and I should be afraid to give a good-sized dose of insulin for fear of bringing about too serious shock.

I wish to support what Dr. Hinsie said about the pattern these patients present. It is a uniform physical pattern. Photographs of the patients all look alike, and the same is true basically of their symptoms. Chief attention is given to the gastrointestinal tract. They will not eat because "it stops right here, doctor [illustrating], and it won't go any further," or "when I eat I feel so bloated," and so on, with the usual story of a gastric neurosis. The fundamental fact is that of the attachment to one or the other of the parents, which Dr. Smalldon mentioned, the unwillingness of the young person to grow up and be an adult. Closely linked is the adolescent, and almost infantile, attitude which the majority present toward sexual matters.

DR. HENRY ALSOP RILEY: I have read numerous articles, that of Dr. Pardee and others, and have seen a number of these patients, but I have never encountered

the condition in a male. So far as I know, I have never seen any reported cases of the syndrome in a male. Can you throw any light on that, Dr. Smalldon?

DR. FRANK J. CURRAN: I should like to know the racial background of these patients. I have seen 5 or 10 such patients in Bellevue Hospital, all adolescent girls, and it is my impression that they were all Jewish. I am wondering whether Dr. Smalldon's patients were Jewish, in view of the fact that the percentage of Jewish patients in Bellevue Hospital is usually not large.

I take exception to the speaker's using the term "mental cachexia." When I read the program I thought he might be going to talk about mental deficiency. There is a recognized name for this condition, and I think it should be used.

DR. JOHN L. SMALLDON: To answer Dr. Curran first, all of these 6 patients were of Anglo-Saxon stock; I have seen no patients with this condition among Jews.

In answer to Dr. Riley, several cases of the disease in males have been reported in the literature. Each author has referred to the fact that such cases are uncommon, and I myself have seen no males with this disease.

The question of diagnosis, or the differentiation of the reactions of compulsive-obsessive neurosis and dementia praecox is one that could be argued all night. It is sufficient to state that each of the patients here reported on has been observed daily for months or years by a number of examiners, who have unanimously agreed that each patient is suffering from a psychosis, a schizophrenic reaction.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *President, in the Chair*

Regular Meeting, May 8, 1942

Subconvulsive Electric Shock Therapy: Effect of Varied Electrode Applications. DR. SOLOMON LESSE (by invitation), DR. B. H. GOTTESFELD (by invitation) and DR. H. H. HERSKOVITZ, Norristown, Pa.

In this study we attempted to evaluate subconvulsive electric shock as an agent in the treatment of the psychoses. At the same time we wished to compare the results of different electrode applications in the administration of electric shock therapy. Twenty-four patients were treated three times a week, each patient first receiving six to ten subconvulsive treatments and then ten convulsive treatments. Each subconvulsive treatment consisted of five applications given over a period of three minutes. Six patients received bifrontal applications of the electrodes, 8 patients bitemporal applications and 10 patients biparietal applications. Routine preshock studies and a postshock check-up examination, including roentgenograms of the spine, were made.

The biparietal applications required a current of the lowest voltage acting over the briefest period to produce a grand mal convulsion. The bitemporal and the bifrontal leads required, respectively, increased voltage and exposure for a longer time to produce the same effect. The subconvulsive reactions were produced by a current of minimal voltage acting over the briefest period, the average being 30 volts applied for three-tenths second.

No complications were encountered with subconvulsive therapy in our series of 24 patients, which confirms the belief that complications are materially reduced with this type of shock therapy. However, in larger series of patients complications may be demonstrated.

In order that the confusion of multiple terms, such as abortive reactions and convulsive equivalents be avoided, it is suggested that the all-inclusive term subconvulsive reaction be applied to those responses characterized by a single severe muscular contraction associated with the prolonged period of unconsciousness

(thirty seconds to fifteen minutes) and the petit mal reactions. With subconvulsive therapy, one may obtain primarily a series of petit mal reactions. However, as the voltage and the time intervals are increased the subconvulsive phenomena become more pronounced.

It seems apparent from our study that subconvulsive therapy does not produce any notable therapeutic effect. Fifty per cent of the patients had affective disorders (5 had manic-depressive psychoses; 3, agitated depressions, and 4, involutional melancholia, and none of these persons improved or recovered with subconvulsive shock doses, whereas 7 patients, or 29 per cent of the series, improved or recovered with convulsive therapy. There were 12 patients with schizophrenia—9 with the catatonic type, 2 with the simple type and 1 with the paranoid type. None of these benefited from subconvulsive treatment, while 2, or 8.3 per cent, improved with convulsive therapy (both patients relapsed soon after treatment was terminated). These results are in contrast to those reported recently by Androp (*Psychiatric Quart.* 15:730-749 [Oct.] 1941).

Our studies further reveal that subconvulsive therapy increases the fear and apprehension patients have for electric shock treatment. Fifteen of the patients showed a definite fear reaction after the applications. Furthermore, an attempt to maintain with subconvulsive applications the improvement shown with convulsive doses failed.

Although one may try subconvulsive doses in treatment of patients with associated hypertension, advanced age, cardiovascular-renal disease or general arteriosclerosis, the results are indeed dubious. Patients may show temporary improvement in ward reactions, but even this is uncertain.

In conclusion, subconvulsive electric shock therapy is of doubtful value. None of the 24 patients in this series treated at the Norristown State Hospital improved or recovered with subconvulsive electric shock therapy, whereas 37 per cent improved or recovered under convulsive therapy.

DISCUSSION

DR. JOSEPH F. HUGHES: Dr. Lesse and his associates have brought important clinical facts to our attention. To obtain clinical results with electric shock therapy, sufficient strength of current must be used to produce convulsive seizures. Experience at the Pennsylvania Hospital for nervous and mental diseases is in agreement with that of Dr. Lesse in that subconvulsive doses are therapeutically ineffective.

This paper raises an important question: How does electric shock treatment stop the psychotic attack? Electroencephalographic tracings following such treatment show that the brain undergoes decided electrical reorganization. Histologic studies on experimental animals and on the brains of 2 patients (Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, *ARCH. NEUROL. & PSYCHIAT.* 47:385-398 [March] 1942) revealed that small petechial hemorrhages and cellular destruction occur in the brain after electric shock therapy. This observation suggests that clinical recovery results from the destructive activity of the electrical current. Such a hypothesis assumes that psychologic reactions following electric shock therapy are incidental to recovery. This hypothesis, for which I take responsibility, has some experimental observations to support it. It is useful only if it serves as a framework for further clinical and laboratory research into the problem of how electrical shock produces recovery from the psychosis. It is a step in the direction of correlating the clinical results with the observed changes in the brain.

DR. B. H. GOTTESFELD, Norristown, Pa.: A series of 27 patients treated similarly has been reported on by Kalinowsky (*New York State J. Med.* 41:2210-2215 [Nov. 15] 1941). Although his results were not identical with the observations in our series, the general trend was practically the same, the responses of 22 patients were in complete accord with those we observed. However, 5 patients improved with subconvulsive therapy. The early report by Kaplan indicated some

improvement with subconvulsive therapy and adjunctive barbituate therapy. The observations in our series did not include the use of adjunctive chemotherapy.

DR. SOLOMON LESSE, Norristown, Pa.: One might ask why we chose to give five applications of the electrodes with each subconvulsive treatment. This was done with the hope that in this manner we should approximate the effective dose given with the convulsive application and at the same time obtain results comparable to those received with regular therapy. In other words, this mode of treatment is more or less empiric. In some instances patients had a grand mal seizure with the third or fourth application of the electrodes, which indicated a cumulative effect induced by repeated subconvulsive doses given within two or three minutes. Even this, however, did not alter our results.

Use of Adrenal Cortex Extract in Cases of Insulin Shock Complicated by Pulmonary Edema: Review of Literature and Report of a Case. DR. B. H. GOTTESFELD, Norristown, Pa. (by invitation).

The purpose of this work is to evaluate the treatment of acute pulmonary edema associated with insulin shock therapy. In a review of 272 cases of schizophrenia, acute pulmonary edema occurred as a complication in 1.1 per cent of cases in which insulin was used. The symptoms of acute pulmonary edema, as outlined by Furst and Goldman, did not follow a fixed pattern in this series. The sequence of events showed considerable variability in the neurologic signs which developed. However, the early forerunner of pulmonary edema was a decided increase in the respiratory rate, followed by labored breathing and cyanosis. There was no constant correlation between the dextrose level in the blood and prolonged coma with or without pulmonary edema.

REPORT OF CASE

C. K., a 20 year old man, had acute symptoms of schizophrenia of two months' duration. He suffered from auditory hallucinations of a condemnatory type and saw visions of God. At times he was mute and resistive. A strong depressive component was associated with his hallucinations, for which electric shock therapy was begun. Ten treatments resulted in some improvement in his adjustment in the ward.

Insulin shock therapy was begun on Nov. 11, 1941. The initial dose of 20 units was increased by 20 units daily. On the seventh day of treatment he received 135 units of insulin. At 11:10 a. m. he entered a state of wet coma, and at 11:50 a. m., without having been tube fed or given medication, he became extremely cyanotic. Almost immediately, bubbling rales could be heard throughout his chest, and frothy sputum began to escape from his mouth. His temperature rose to 105.8 F. The blood dextrose was 520 mg. per hundred cubic centimeters. The respiratory rate rose from 48 to 70 per minute, and cyanosis was extreme.

Neurologically, the patient showed bilateral Babinski and Tromner signs. The deep tendon reflexes were uniformly exaggerated, and the corneal reflexes were absent. The pupils were dilated and reacted sluggishly to light.

The plan of treatment was to administer oxygen, adrenal cortex extract, thiamine hydrochloride in large doses and supportive measures in the form of digalen and fluids as indicated. He received 10 cc. of adrenal cortex extract, divided into three doses administered at three hour intervals. Later, he received sulfonamide drugs, with the idea of preventing a complicating pneumonia.

The symptoms of pulmonary edema persisted for fifty hours, and he remained in coma for seventy-four hours. On the fourth day he began to speak, but his speech was so slurred as to be unintelligible. The Babinski sign disappeared, and the corneal reflexes returned. However, he was hypersomnolent, and the soft palate was partially paralyzed. For two weeks he appeared dazed and "washed out." Improvement was constant, and he no longer revealed any evidence of hallucinations. The Babcock-Levy test revealed an efficiency index of —5.5, and this extreme degree of pathologic inefficiency led one to believe that the

patient had sustained organic damage to the brain. The Rorschach test revealed no signs of organic disease, but indicated strong schizophrenic tendencies.

CONCLUSIONS

1. Acute pulmonary edema was found in 1.1 per cent of the patients with schizophrenia who were treated with insulin at the Norristown State Hospital.

2. The occurrence of neurologic signs with acute pulmonary edema did not, in all cases, follow the pattern associated with insulin shock therapy.

3. Adrenal cortex extract proved of value in the treatment of acute pulmonary edema and prolonged coma associated with insulin shock therapy.

DISCUSSION

DR. THURSTON D. RIVERS: I have listened with interest to the paper because in my experience I have not observed pulmonary edema as a complication of prolonged stupor.

I wonder why Dr. Gottesfeld thinks that the administration of saline solution, as well as adrenal cortex extract, to patients with this condition is beneficial. It seems to me that any increase of blood volume, with a tendency to dilate the blood vessels, would be contraindicated. The use of adrenal cortex extract will probably have some effect on the water balance, but I do not see how it would increase the ability of the cells to utilize the sugar in the blood stream.

DR. ARTHUR P. NOYES: What would you think, Dr. Rivers, of the advisability of using plasma or of the transfusion of whole blood?

DR. THURSTON D. RIVERS: Hypertonic solutions of all kinds may be useful. Whole blood has some dehydrating effect, but not a great deal. The use of dry plasma, dissolved in 50 per cent sucrose, should be beneficial.

DR. SOLOMON LESSE, Norristown, Pa.: The extent of damage to the brain done by prolonged coma is still a question. Dr. Harry Zimmerman, of Yale University, has told me of a woman of 44 with schizophrenia who died after four days of prolonged coma occurring in her second course of insulin shock treatment. At autopsy her brain showed extensive destruction of the ganglion cells.

DR. THURSTON D. RIVERS: It is well to consider prolonged stupor not so much as a complication but as an extension of the desired period of coma. A patient with prolonged hypoglycemia should first be treated with dextrose if he reaches the condition in which dextrose does not seem to be restorative, other therapeutic measures, such as administration of plasma, should be instituted. Then there are persons who respond to no therapy whatever. I have been much interested in patients with prolonged coma and their recovery. In my own series I was surprised to find that only 50 per cent of the patients with prolonged coma were benefited by the coma.

DR. B. H. GOTTESFELD, Norristown, Pa.: The association of pulmonary edema and other pulmonary complications with prolonged coma is not uncommon. Jessner indicated that pulmonary complications constitute one of the more frequent types of untoward reactions to insulin treatment. As to justification for the use of saline solutions following pulmonary edema, I should like to point out that there is considerable difference of opinion. The use of plasma and whole blood has been recommended. The theory that there is increased vascular permeability remains to be proved. The question arises: "Why should there be increased local pulmonary permeability without any evidence of peripheral edema or increased peripheral vascular permeability?" The problem may be concerned with the parasympatheticomimetic factors controlling the pulmonary vasculature.

Numerous reports on cerebral complications may be found in the literature. Freed and Sachs, Wortis and others have described vascular changes associated with prolonged coma. In my study I attempted to correlate the performance test with the changes produced by the prolonged coma and the associated pulmonary

edema. Further studies at three month intervals will aid in determining the degree of recovery.

The Rorschach Method in State Hospital Practice. DR. E. LOUISE HAMILTON, Norristown, Pa. (by invitation).

The Rorschach method is a projective technic which is being used with increasing frequency in mental disease hospitals and in child guidance work. My associates and I have found it extremely useful in cases of difficult diagnosis in both the Norristown State Hospital and the child guidance clinics conducted by the hospital. The technic devised by Dr. Hermann Rorschach, a Swiss psychiatrist, consists of ten standard ink blots, five black and white and five colored.

The procedure consists of three parts: performance proper, inquiry and testing of limits. The scoring is not simple. There are fourteen scores for location, or the part of the blot used. There are also twenty-nine determinants, such as form, movement, color and texture. Content and popularity or originality of the answer are other types of scores. Interpretation of a Rorschach record is a highly skilled task and requires considerable training and experience. It is not possible to draw conclusions from any one factor unless they are confirmed by other factors.

Three cases are presented in which the Rorschach technic was especially helpful in the diagnosis and in the disposition of the patient. In 1 of these cases the patient was thought to be almost entirely recovered after a series of insulin treatments and prolonged coma with pulmonary edema. The Rorschach test showed that he had not recovered sufficiently to resume his former occupation. The results of the Babcock test agreed with those of the Rorschach method. Recommendations were made that he find a simpler type of occupation. Another case was that of a patient about the diagnosis of whose condition there was considerable disagreement. Traumatic psychosis, schizophrenia and manic-depressive psychosis were all considered. The Rorschach results did not reveal anything of a schizophrenic or organic nature and seemed to indicate that the patient had had an affective reaction. His condition was finally diagnosed as manic-depressive psychosis, and he later recovered and went home. Another case was that of an adolescent boy of 17 years whose condition had been diagnosed in another clinic as schizophrenia, but the Rorschach test seemed to indicate that he was not especially different from the average 17 year old boy who has not yet solved some of his sexual conflicts. Later, after a short period of treatment in the child guidance clinic, he found a job. According to recent reports, he is adjusting well in the Army.

Testosterone Therapy of Involutional Psychosis. DR. E. F. KERMAN, Norristown, Pa. (by invitation).

In this study, 12 male patients with involutional melancholia were treated with testosterone propionate. There are several reasons that this work was undertaken. First, conflicting reports have appeared concerning the value of testosterone in cases of involutional psychosis in males. Results in the various investigations range from 100 per cent recovery to no improvement at all. Second, the number of cases cited in the literature is small, and it was felt that further work would aid in the statistical evaluation of the efficacy of the drug. Third, the dose employed by other workers, usually 10 mg. three times weekly, has been questioned, the suggestion being given that 25 mg. is a more effective amount. The latter dose was employed in this study.

All of the males admitted to the Norristown State Hospital in the past five years whose condition had been diagnosed as involutional psychosis were considered for treatment. Of this group, there were 12 for whom the diagnosis was clear and whose symptoms had remained constant for a period sufficiently long that the likelihood of a spontaneous remission during the period of treatment was minimized. The ages of the selected patients at the onset of their illness ranged from 53 to 64 years. The duration of the psychosis varied from one and a half

to five years. Other treatments had been employed previously with 5 of the patients. Full courses of metrazol given to 2 of these 5 patients brought about no change. With 2 others convulsive shock therapy had been tried but had to be terminated because of cardiac decompensation resulting from treatment. In 1 patient narcosis had been induced with sodium amytal, with no improvement. Practically all of the men were poor risks for shock therapy because of their age or physical condition.

Testosterone propionate, in ampules containing 25 mg. in oil, was injected intramuscularly three times weekly for thirteen weeks. The patients were not told the nature of the treatment or its purpose. No effort at psychotherapy was made. The patients were then observed for two months and again given testosterone for seven more weeks. They were observed for two months after this. In all, this study covered a period of eight months, and each patient received a total of 1,500 mg. of testosterone propionate.

Of the 12 patients, 11 showed no improvement whatever either during or after treatment. Two of the 11 patients showed increased agitation during treatment, which subsided considerably afterward. One patient improved. He was 56 years old at the onset of his psychosis three years before. About a month after treatment was started, he began to take an interest in ward work. He continued to show improvement, and seven months after the beginning of testosterone therapy the staff of the hospital considered him well enough to grant the request of his family that he be allowed to return home, where he is at present.

The results, therefore, show 1 case of improvement among 12 patients. One cannot say whether the improvement in the 1 patient was due in any measure to the testosterone or whether it was coincident with treatment. Since the course of the majority of the patients was unaltered by the substance, it seems that one can state with reasonable assurance that testosterone propionate appears to have little or no effect in the treatment of involutional melancholia in the male.

Psychosis Associated with Progressive Muscular Dystrophy. Dr. B. H. GOTTESFELD and Dr. H. H. HERSKOVITZ, Norristown, Pa.

The case here reported concerns the development of dementia praecox in a single white man aged 24 who suffered from progressive muscular dystrophy. He has a brother who is not psychotic, but has progressive dystrophy, and a twin sister who has escaped both diseases.

The family history is without significance. The mother died when the patient and his twin were born. The twins were raised by the maternal grandparents, while the brother was brought up by the paternal grandparents. After his wife's death the father took little interest in the children. He was said to have been ashamed of his sons because they were crippled. The patient was described as kind, gentle and obedient. He liked to read poetry, philosophy and books on etiquette. In both brothers the onset of muscular dystrophy occurred at the age of 8 years, and weakness progressed gradually. Our patient was fearful of becoming dependent on others and did everything he could to better himself. Although working under a great handicap, he graduated from high school. He took a business course, with the hope of later supporting himself. Home conditions were rather poor in that the people with whom he lived were unsympathetic. He considered them vulgar and disliked their profanity. The patient's brother was always shielded by his grandparents. He took little interest in school. His grandparents did not permit visitors because they did not want the boys "gawked at." Long before the patient consented to wear crutches his brother was spending all of his time in a wheel chair. The patient's psychosis occurred suddenly. He expressed the belief that he was poisoned; he heard voices of a condemnatory nature and was loud, destructive and assaultive.

The pertinent literature is reviewed. The difference in the prepsychotic personality of the patient and that of his brother and the possible reasons for the development of a psychosis in the patient are discussed.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding**Regular Meeting, May 14, 1942***Potentials of Rapid Frequency in the Human Electroencephalogram.**

DR. KNOX H. FINLEY.

Gibbs in 1937 described the range of frequencies of the bioelectric potentials of the brain as the "cortical frequency spectrum." This spectrum may be divided into three bands: (1) slow, 1 to 8 cycle per second waves; (2) medium, 8 to 12 cycle per second waves, and (3) rapid, 12 to 40 or more cycle per second waves. This study is concerned with those cycles of rapid frequency which have an amplitude of 25 microvolts or more. Most of these cycles are within the 18 to 30 per second range of the rapid frequency band.

Although these high voltage, rapid cycles occurred in a small percentage of electroencephalographic tracings from normal control subjects (less than 5 per cent), they appeared in a significantly higher percentage of tracings from over 4,500 persons representing a variety of neuropsychiatric disorders. Three inferences are to be made from this study: (1) Rapid frequency patterns are widely distributed throughout the neuropsychiatric disorders; (2) similar types of rapid frequency patterns are encountered in a variety of clinical conditions, and (3) various types of rapid frequency patterns are to be found among patients with the same clinical condition.

Gibbs, in his studies on epilepsy, was the first to call attention to a certain type of rapid activity. Because he was impressed by its frequent occurrence in cases of grand mal epilepsy he termed such activity "grand mal activity." In my experience similar activity is encountered with a variety of clinical conditions, and even more often with neurosyphilis and affective psychoses than with grand mal epilepsy.

DISCUSSION

DR. FREDERIC A. GIBBS: Some of Dr. Finley's remarks were aimed so directly at me that I can hardly escape the necessity of replying. The tremendous number of cases that he has studied entitles him to speak with authority not only on the psychoses but on epilepsy.

My associates and I have good precedence in electroencephalography for the use of clinical and electrical terms interchangeably. The clinician is interested not in a neurophysiologic interpretation but in clinical correlations. We find it convenient to abbreviate the statement "3 per second wave and spike activity of the type most commonly seen during petit mal seizures" to "petit mal type of disorder," and similarly for grand mal and psychomotor seizures. Dr. Finley has said that what is called grand mal activity is not seen most commonly with grand mal seizures. It is possible that we have used this term too loosely and have misled him. We have always made a distinction between more or less steady fast activity and true grand mal activity. We have tried to reserve the term "grand mal" for a discharge of the type which is seen at the time of a grand mal seizure, just as we have reserved the term "petit mal" and "psychomotor" for the type of activity seen during petit mal and psychomotor seizures. It is true that grand mal discharges are rare in interseizure records, but we have never encountered a grand mal discharge in the tracings of more than 3,000 normal control subjects or in those of more than 4,000 patients with neuropsychiatric disorders unassociated with epilepsy. The latter group represents every type of disorder which Dr. Finley has studied. All recognize that the electrical activity of the cortex as it appears in the electroencephalogram is exceedingly complicated. There are many ways in which to regard it. If it is looked at in our way, certain definite correlations can be found between epilepsy and special types of seizure patterns. I cannot believe that Dr. Finley wishes to deny these correlations. They are as

real as anything in electroencephalography and as good as many of the most important correlations in clinical neurology. If any one wishes to use different words, "rapid activity" instead of "fast activity," "spike and wave" instead of "wave and spike" or "abnormal waves" instead of "dysrhythmia," that is immaterial, but the facts remain; they are as we have stated them, and they can be seen by any one who has requisite powers of discrimination.

DR. ROBERT S. SCHWAB: Dr. Finley's paper is important because it emphasizes a band of frequency often disregarded in the localization of tumors and in the study of cerebral disorders. My first contact with fast frequencies came in a case in which from a localized area of 3 to 4 cm. there was a continuous discharge with a frequency of about 18 to 26 cycles. One of my associates suggested that this looked like a muscle discharge, though it was above any muscle. It was not present on the other side. The patient had jacksonian convulsions, and operation, which was eventually performed at the Massachusetts General Hospital, revealed an infiltrating glioma. We often wheel the portable electroencephalograph into the operating room for direct recording from the exposed brain. In this case the same fast frequency was picked up from the tumor, but was not picked up 5 cm. away from the infiltrating tumor in normal cerebral cortex. Therefore we were sure that this was actually a cerebral discharge. Dr. Finley did not emphasize that this fast frequency looks like that of muscle. In the particular case I cited we eliminated the possibility of this fast frequency's being from muscle. Sometime later Dr. Madelaine Brown and I, in examining a group of patients with Ménière's disease, encountered a frequency which resembled that of muscle. Our final conclusion was that there is, in patients with intense vertigo of Ménière's type, a fast frequency discharge from the cortex that looks something like a muscle potential. But I do not think one can be certain that there is not some muscle discharge in these tense patients when they are suffering from attacks of vertigo. Further evidence that would verify the assumption that these discharges are really cerebral and related to an abnormal cortex I observed during operation on 4 patients with Parkinson's disease. In all 4 patients I noted increased voltage and increased fast activity from the cortex in a region where there was no muscle within 6 cm. of the electrodes. At the time of the first observation of this fast frequency, I suggested to the neurosurgeon that this was an abnormal discharge and that he had better use a weak current for stimulation. This he did not do, and in two or three minutes the patient had a generalized seizure on the operating table. This happened a second time with another patient who showed high frequency waves with cortical stimulation; so I am convinced and I agree with Dr. Finley that such fast frequencies do occur in the cortex. I have seen them on six occasions in the operating room. One must be careful, however to eliminate muscle frequencies, which parallel this band closely.

DR. FREDERIC A. GIBBS: I should like to spare Dr. Finley from having to defend himself against the imputation that he may have confused fast activity of cortical origin and muscle potentials. A beginner might make such a mistake, but any one with a good instrument and sufficient experience will be able to distinguish certain types of fast activity which are not that of muscle. I am sure that Dr. Finley can do this and that in what he has said about rapid activity he referred to a type of activity which is clearly distinguishable from muscle activity.

DR. WILLIAM G. LENNOX: Dr. Finley deprecated the practice of not using a sufficiently large "gain" so that abnormal waves are clearly discernible. I should criticize his slides for the same reason. With so many tracings on a single lantern slide, each tracing is so small that we of the audience are unable to judge whether his rapid waves are from brain or from muscle. Also, he did not show samples of rapid activity from his normal group.

DR. KNOX FINLEY: I disagree with Dr. Gibbs's statement that the clinician is not greatly interested in neurophysiologic interpretations. It is this very interest that makes the clinician so critical of Dr. Gibbs in his use of clinical terms

in interpreting his neurophysiologic data. The clinician is aware of the limitations of these clinical terms and has reason to be skeptical. Dr. Gibbs has stated that perhaps he has used the term "grand mal activity" too loosely, and that it should be limited to a discharge of the type which is seen at the time of a grand mal seizure. In my experience "grand mal activity" varies even during a grand mal seizure. Furthermore, activity of the type occurring during grand mal attacks is by no means limited to grand mal epilepsy, but, as I have shown, is associated with other neuropsychiatric disorders. There must of course exist some correlation between epilepsy and special types of seizure patterns. From my own studies I am not clear as to what these correlations are; furthermore, I am unable to confirm the special correlations which Dr. Gibbs finds, or at least implies.

Dr. Schwab has raised the question of one's confusing rapid activity with muscle artefact. The two may be confused if one does not use the necessary precautions. There are several ways of ruling out muscle as the source of the rapid activity, which I have described this evening. For example, these rapid frequency cycles of cortical origin are often better brought out by the bipolar technic, in which the electrodes are more removed from the source of muscle, than by the monopolar technic, in which the indifferent electrode lies near muscle tissue. In cases of neurosyphilis one sees these rapid cycles disappear with anti-syphilitic treatment and clinical improvement. Furthermore, rapid activity of cortical origin is sometimes seen in the early stages of physiologic sleep, when the subject is well relaxed.

Dr. Lennox criticizes the amount of gain used in the samples illustrated in the lantern slides. Most of the samples shown were amplified two or three stages, which I believe is in keeping with the amount of gain Dr. Gibbs and Dr. Lennox often use in their laboratory. My lantern slides were not made up to establish that these rapid waves were from the brain rather than from muscle. As Dr. Gibbs has already stated, with a little experience and care one need not confuse a muscle artefact with rapid potentials. The rapid patterns which occurred in the tracings of a small percentage of my normal group were sufficiently similar to those illustrated in the lantern slides that, in the time allotted, I did not feel justified in duplicating them.

The Kenny Method of Treatment of Infantile Paralysis. DR. ARTHUR L. WATKINS.

The National Foundation for Infantile Paralysis has recently sponsored in Minneapolis a course for physicians to demonstrate the Kenny method of treatment and to present for evaluation the original cases in which the treatment was employed. My conclusions are based on evidence presented in this course.

The traditional treatment of poliomyelitis, although not standardized, will be outlined briefly for comparison. It is generally believed that flaccid paralysis develops from destruction of anterior horn cells, but in some instances certain groups of muscles are less affected and tend to cause deformities by imbalance. Splints are therefore applied to prevent this and to rest the affected muscles. When muscle tenderness has disappeared, active reeducation of weak muscles is started, the splints remaining on between treatments. There is great variation, however, in the time of starting motion and in the use of local heat and hydrotherapy.

The Kenny method of treatment is based on a different concept of the symptoms and the factors which lead to the development of deformities. Miss Kenny recognizes that there will be a certain variable percentage of patients with residual flaccid paralysis of one or more extremities. This is a result of complete destruction of anterior horn cells, for which no cure is known, nor does she claim any. Miss Kenny's treatment is directed toward another condition which she calls muscle "spasm." This symptom is thought to be of the utmost importance, for if it is not treated early, contracture, fibrosis, atrophy and loss of function will result. This so-called spasm consists in pain, tenderness on

pressure, constant hyperirritability, particularly on stretching, and in some cases visible fasciculation. After several weeks muscles which have been thus affected and not treated properly will exhibit contracture, fibrosis and atrophy. Kenny's term "spasm" refers in a general way to these conditions and is misleading if interpreted according to general usage.

Miss Kenny has further observed that in the majority of cases the posterior muscles of the neck, trunk and lower extremities are more affected by "spasm" than the anterior muscles with antagonistic action. She believes that if treatment is carried out in the traditional manner the antagonists of the muscles with "spasm" become lengthened and atrophied from disuse and that finally power of voluntary contraction is lost. She designates such a functionally paralyzed muscle as "alienated." She also speaks of it as "nonparalytic," which means that if the "spasm" of the antagonist is released and the muscle is allowed to regain its proper resting length, it may be made to function by proper stimulation and reeducation. She has learned to distinguish a truly paralyzed muscle from an "alienated" one by passively stretching the muscle a few times within a small range of motion; then, by careful observation, a functionally paralyzed muscle will be seen to become tense, so that its tendon will stand out beneath the skin. One might explain this by the assumption that the myostatic stretch reflex had thus been elicited.

A third factor leading to muscular dysfunction Miss Kenny has called "incoordination." This consists in the substitution of accessory muscles, or even antagonists, for the proper prime movers of a joint. Individual muscles also are said to contract improperly in sections rather than through their full length; again, this is spoken of as "incoordination." This phenomenon, I believe, is generally recognized to occur whenever there is attempted motion with partially paralyzed muscles around a joint and also when the joint is immobilized.

The Kenny method of treatment aims to eliminate or correct these three factors leading to deformity and impaired movement. The muscle "spasm" must be treated as soon as the diagnosis is made. A delay of as little as three or four weeks may seriously compromise the results. Treatment consists in the application of hot packs of a measured size to fit muscles without immobilization of the joints. These woolen packs are immersed in boiling water, wrung out twice through a tight wringer at the bedside and applied quickly to the involved part. The pack is then rapidly covered with oiled silk and a layer of dry flannel. The packs are changed every fifteen minutes if spasm is acute; otherwise, every two hours for a twelve hour period each day. Spasm is usually relieved within a week by such treatment, but packing is continued for weeks or months if the muscle exhibits contracture or shortening. Although the original temperature of the pack is high, there is rather rapid cooling, and at the end of two hours there is probably a tendency for the body to heat the pack. This is in reality, then, a type of contrast therapy.

No active or passive movements which cause any spasm or pain are allowed. When the spasm is relieved, passive motions only are started while the packs are still in use, and the muscles are said to be "stimulated" by this. One might interpret this physiologically as the setting up of a barrage of proprioceptive impulses to facilitate the motor pathway and the proper pattern of response. Active motion, or muscle reeducation, begins only when spasm has been relieved. This may be within a week in some cases, while in others some muscles may exhibit residual spasm which requires hot packs for months.

Miss Kenny's system of muscle reeducation emphasizes the isolated action of certain important muscles for each movement of a joint. The patient is taught exquisite control of agonists and antagonists so that smooth rhythmic motions are obtained. There is no effort to strengthen individual muscles by resistive exercises, but the purpose is to increase strength by repeated coordinated movements. All the patients I saw there were beautifully trained in the performance of these motions and were flexible to a degree rarely seen in average normal persons.

The most convincing evidence available at present in favor of the theory that muscle spasm if untreated leads to contracture deformities is obtained by comparing the patients treated by the Kenny method with others in the same epidemic who were treated early by immobilization without packs. Whereas in the first group there was complete freedom of motion in all joints through a normal range, in the latter group a mild or severe degree of stiffness and contracture could be demonstrated, particularly of the posterior muscles of the back and the lower extremities.

The nature of muscle "spasm" is unknown, but several possibilities will be investigated in the future. In a recent case my associates and I have observed abnormal electrical activity as judged by the electromyographic tracing from an involved muscle. In another case of long standing, an apparently paralyzed muscle responded well to faradic stimulation, an observation suggesting that functional paralysis may occur in this disease.

It is extremely difficult to evaluate statistically the results of treatment of different groups of patients with poliomyelitis because of the variability in the extent of paralysis which is to be expected. Eighty-four patients in the early stage have been treated in Minneapolis by the Kenny method. Among these patients there were residual paralyses in 10 lower and in 2 upper extremities. Although all patients showed involvement of muscles of the neck and back and the hamstring muscles, in no instance was there residual involvement of the trunk. The most striking feature observed in these patients was the ease and coordination of movement and the remarkable suppleness. None of the familiar contracture deformities were seen, and the condition of the skin, subcutaneous tissues, muscles and joints in the paralyzed extremities was better than is usually seen as judged by inspection and palpation. Although no splints or supports were used while "spasm" was present, they were not objected to after the period of recovery. No deformities resulting from this lack of immobilization were observed. The comfort and morale of patients under treatment were impressive.

In summary, the following conclusions are stated:

1. In acute poliomyelitis "spasm" of affected muscles is a condition of undetermined cause, which if untreated leads to contracture deformities, functional paralysis of antagonistic muscles and dysfunction of accessory muscles.
2. Muscle "spasm" is relieved by the application of hot packs as described if treatment is started within the first week or two of the illness.
3. Functional paralyses are prevented by elimination of spasm of antagonists, and by stimulation of proprioceptive impulses through passive movements.
4. Smooth, coordinated movements are developed by a system of muscle reeducation stressing isolated muscle action.
5. Contracture deformities have been eliminated without the use of splints.
6. Functional results are equal or superior to any known method of treatment, although residual flaccid paralysis is not eliminated.
7. Similar results have been obtained by many different users of this method of treatment.

DISCUSSION

DR. FRANK R. OBER: I had heard a great deal, both pro and con, about Miss Kenny's method of treating infantile paralysis. Last autumn, I made a visit to Minneapolis and spent a day with her at the clinics, and had a very interesting time.

In 1915 Dr. Lovett and I began the use of hot packs and hot baths in the early treatment of infantile paralysis, but of course most of our patients did not come to us until several weeks after the quarantine period was over. We found that with the use of hot packs and baths the patients with deep sensitiveness were made more comfortable; we also noticed that they could move their legs in a hot bath when it was impossible to do so on a bed.

Of course Miss Kenny's treatment is an all day affair, in which she bakes the legs in hot fomentations by a special technic, and there is no question that the

sensitiveness and muscle spasm disappear much more rapidly than with the standard therapy. She states that contractures and spasm and limited motion in joints occur as a result of prolonged immobilization. I have seen these phenomena many times even when there was not much paralysis present.

Personally, I have adopted the practice of applying wire splints to the extremities when they are in the position of comfort and of using the hot packs or hot baths three times a day, and I have found that the flexed extremities will relax and gradually straighten out. The wire splints have the advantage over plaster casts in that they can be bent to follow the line of deformity as the leg improves.

There is one element in poliomyelitis that is confusing; that is, tenderness and pain in the nonparalyzed extremity may be even greater than in the paralyzed extremity, and sometimes it takes a long time for the nonparalyzed extremity to be relieved of the pain. It has been our experience that deep massage always increases the tenderness and deformity, the latter being due to the spasm of the muscles.

Patients with poliomyelitis appear to be perfectly comfortable in bed until some one tries to do bed nursing; then it is found that the legs, the arms or the back is sensitive. Sensitiveness may be elicited by straight leg-raising, muscle squeezing, dorsiflexing the calf or putting any of the flexor muscles on the stretch. If the leg is allowed to assume a bad position, contractures may develop which will be difficult to straighten out.

If one is to use the Kenny treatment, it must be carried out thoroughly; otherwise, one must prevent deformities by other methods which are known and fairly well standardized. In Sister Kenny's cases, however, there does not seem to be the atrophy which occurs from prolonged splinting. I found in her cases that the skin was in excellent condition, with apparently normal color and normal circulation. If immobilization is to be given up entirely, the nursing care must be of the best.

I believe that the early application of heat as advocated by Sister Kenny is a distinct advantage in the treatment of infantile paralysis and that with this method the deep pain and spasm disappear much more readily than with the older methods of prolonged immobilization and lying in bed.

DR. D. E. DENNY-BROWN: I agree entirely with Dr. Ober's impression. Miss Kenny's treatment was the subject of two committee reports in Australia in 1936. It was the impression of those committees that her success was due to the intensity rather than to the nature of her system. Perhaps an orthodox method, used as intensively, would have been as good. In 1937 she went to England and was given three wards, a treatment clinic, all the apparatus she wished and five whole time masseuses. The original plan was to review the situation after three months, but the period was extended to a year. At the end of that year a combined committee of neurologists and orthopedists made a report. At that time she had not evolved the present rationalization of her method. Spasm was not then an important factor, nor was "alienation." At that time, too, she claimed that if her treatment was started sufficiently early, a complete "cure," as she termed it, could be obtained. The validity of that assertion was denied by the committee, who found that her claim of effecting a complete cure was not substantiated. She has since dropped this claim and recognizes that persistent flaccid paralysis is sometimes encountered. It was found that her methods of hydrotherapy were valuable and did no harm, but the committees were not convinced that very early application of them, or of passive or attempted active movements, was essential. My own histologic experience in observing torn muscle fibers in the early stages of the disease certainly gives me great respect for recently paralyzed muscle. It was found by the committee that splints can often be dispensed with in the early stages, but are sometimes valuable and essential. It was further felt that at that time Miss Kenny had begged the question of subsequent deformity and was not capable of dealing with the mechanical situation resulting

from persistent paralysis. I should like to ask what happens now with respect to the late stage of such paralysis, for Miss Kenny has modified her views considerably since then.

Unfortunately, Miss Kenny would have none of any method that attempted to combine other, most useful measures with her therapy, and so to her the world was divided into those who would accept her treatment in every small detail and those who would not. Most workers prefer not to be driven to one extreme in every detail or to apply a rigid routine in every case. Dr. Ober expressed it perfectly when he said there was no such thing as an orthodox method.

I am intrigued by the question of "spasm," or "spasticity," and I should like to ask whether by the term Miss Kenny refers to rigidity of the neck and to resistance to movement in the neck and shoulders, particularly in the early stages of paralysis. Many investigators have noted that long after the spinal fluid has returned to normal, or has shown only an increase in protein, there is often persistent rigidity of the neck. I myself had attributed this symptom to the fact that the spinal cord was still inflamed. Might this condition of "spasm," therefore, be central in the sense that tension on meningeal attachments causes "spasm," without any reference to lesions in the muscles? In that case, would not the hot packs and heat be better applied to the spine than to the affected muscle?

DR. JAMES B. AYER: I agree with Dr. Ober that there must be value in the Kenny treatment. At the Massachusetts General Hospital, my associates and I felt strongly enough about this treatment to send Dr. Watkins to Minneapolis, where he spent a week. He has come back enthusiastic. If an epidemic of poliomyelitis occurs, we plan at the hospital to place certain patients under this treatment and to study them with reference to certain laboratory tests which are not being used at Minneapolis, particularly electromyographic studies. I was especially interested in a remark made by Dr. Smith-Petersen, who, when asked his opinion of this treatment, said: "After all, orthopedists do not all have set methods of treating this disease. Many do use fomentations now and carry out active muscle training in the early stages." In any case, Sister Kenny has emphasized active therapy in the early stages of paralysis, and the results obtained justify reevaluation of the method by persons directly concerned with the treatment of poliomyelitis.

DR. ROBERT SCHWAB: Does Dr. Watkins know of any application of this therapy to disease of the anterior horn cells and muscle atrophy? I wonder whether this method of heat and massage would not be a sensible therapeutic venture in management of fibrillation, which so far has not responded to use of vitamins or other treatment.

DR. H. HOUSTON MERRITT: How expensive is this treatment, and how much nursing care is needed?

DR. ARTHUR L. WATKINS: I think that Dr. Ober and the other discussers are entirely right in emphasizing that there is no one traditional treatment, and Dr. Ober has long pointed out the disadvantage of using massage when one is not careful of the tender muscles. Many people overlook the spasm in muscles. Miss Kenny has changed a great deal in her concepts. They notice it in Minneapolis as time goes on. She learns from the physicians who go out there; so her method is not any one set type of treatment. She states she never saw the bad cases in Australia that she has seen in Minneapolis, and she admits that she does have cases of residual paralysis. While I was there she said, "This person should have some braces and supports and probably some stabilization operations on his feet." She is still rather ritualistic, as in the pack treatment, and I think many observers are not particularly impressed. It seems as though something easier and more effective should be developed. She makes a point of distinguishing between rigidity of the neck and back due to meningeal infection and that occurring in poliomyelitis. She was not able to convince me exactly, and I am still not clear as to what the difference may be. I think the meningeal irritation may be an explanation to some extent, but the mechanism is vague. She does treat the region of the neck and spinal cord.

I do not know whether this treatment has been applied to progressive muscular atrophy. Miss Kenny does not employ massage. The use of heat is directed toward the muscle, although she has applied it in Australia in cases of infantile cerebral palsy for relief of spasticity. As for its effect on fibrillation, that, also, has not been studied.

In Warm Springs, Ga., they have adopted the policy of using ward maids for applying packs, which they can do at a minimum cost. If this were done by the nursing personnel the expense would amount to a great deal.

Toxoplasmic Encephalitis: Clinical Experience. DR. BRONSON CROTHERS.

Toxoplasmic infection as a cause of cerebral and ocular lesions in children was unknown until a series of papers by Dr. Abner Wolf and his associates, in New York in 1937 and thereafter, and by Dr. A. B. Sabin and his associates, in Cincinnati, proved that a significant number of cases existed. Other important papers by Pinkerton and Weinman and Pinkerton and Henderson indicate that adults can also acquire damaging or fatal lesions.

The wide geographic range of the parasite and its many animal hosts make it likely that the distribution of cases of the disease in man is almost universal. Certainly, the cases reported here come from widely separated places, as is usual in hospital and private practice.

Pathologic studies on newborn infants have demonstrated the organism in the eye and in the brain.

The evidence that intrauterine infection takes place is increasingly convincing. The final proof, which could be obtained by identifying toxoplasmas in the placenta, is still absent, but the results of tests of the blood and other observations make the hypothesis defensible.

The evidence certainly suggests that the organism may live for many years and that it carries a serious threat to future children of a mother who has had one infected child. On the other hand, there is no evidence that the infection does not completely die out in most cases. As far as I know there is no report that viable organisms are found in later offspring, although clinical evidence suggests that they may lurk in tissues for years.

The first reports, of course, dealt with the cases of severely damaged infants. In these children hydrocephalus was the rule. It is now evident that certain persons survive without important handicap, even if the infection involves both the brain and the eyes. Furthermore, it is probable that a fair number of children suffer cerebral damage without calcification, and it seems certain that the eyes alone suffer in others. Available evidence also indicates that infection may occur without producing any symptoms or signs at all. In general, it seems clear that calcification may be present without altering the brain bulk or distorting the ventricles in any way.

The development of a method for the recognition of the disease in the laboratory is due to Sabin and Olinsky (*Science* 85:336, 1937). The procedure involves intradermal injection into a rabbit of infected mouse brain mixed with varying quantities of the blood of the suspected person. A high degree of protection is afforded by the presence of the blood of a person who has been infected. Readings are taken after a few days.

The obvious suggestion that certain rabbits are immune and therefore will produce false positive reactions has been followed up, and all objections which occur to me have been met. Ample controls have been used.

Sabin reported that tests on a considerable sample of persons with no obvious infection gave positive results in about 10 per cent. He suggested that these persons might well have subclinical toxoplasmic infection. Certainly the investigation of several families indicates that this hypothesis is reasonable.

In this paper a small series of cases is presented in which a clinical diagnosis of toxoplasmic infection was supported by serologic evidence. All the children were seen at the Children's or at the Infants' Hospital, and none of them was

referred here as having a probable or proved case of the disease. The disease was called to the attention of the staff of the Children's Hospital under the following circumstances:

The first case was that of an intelligent, competent girl of 12 years with choreoretinitis and calcification. She had had a single severe convulsion. Tests for the presence of the organism in the blood of various members of the family made in our laboratory gave the following results: father, negative; mother positive; sister, doubtful; sister, doubtful, and patient, strongly positive.

The second case was that of a 7½ month old girl who had mild hydrocephalus and microphthalmos with calcification. Results of tests of the blood of all members of the family for toxoplasma were as follows: father, negative; mother, positive; brother, positive, and brother, positive.

The third case, seen first in 1929, was that of a girl with convulsions and calcification without choreoretinitis. The tests on her blood and that of her mother have not been completed.

The fourth case was that of a boy with convulsions, choreoretinitis and calcification.

The fifth case was that of a boy, a younger brother of the fourth patient. He had choreoretinitis, hemiplegia and calcification with mental retardation. The results of testing the blood of this family were as follows: mother, positive; brother (case 4), positive; normal brother, moderately positive; brother (case 5), positive; sister, negative, and sister, negative.

The sixth case was that of a girl with choreoretinitis, calcification and convulsions.

The seventh case was that of the younger brother of the preceding patient. He had similar symptoms; the mother had calcification without choreoretinitis, and another sister had calcification but no ocular or mental symptoms. The blood of the mother and these 3 children was reported to be positive for the organism.

The eighth case was that of a boy of 10 years and 7 months who had convulsive attacks, choreoretinitis and calcification. Roentgenograms of the skull of the father, the mother and the sibling were without significance. Tests of his blood and that of his mother gave positive reactions for Toxoplasma.

The ninth case was that of a boy of 4 years and 9 months with mental defect, choreoretinitis and calcification. The mother and a sibling showed no choreoretinitis, but studies of their blood were not possible. The blood of this child was reported to be positive for Toxoplasma.

In the course of this investigation, which was largely an attempt to remember instances of the disease, I have collected 10 cases in which the clinical requirements were fulfilled and serologic reactions were positive. In addition, 8 members of the families represented reacted positively to serologic tests but did not present clinical evidence of the disease.

In 3 other presumptive cases serologic tests are now being made, and 2 others which are clinically typical are being sought for but efficient contact has not yet been established.

DISCUSSION

DR. DAVID H. WEINMAN: Dr. Crothers has described the clinical and roentgenologic features of infantile toxoplasmosis. Toxoplasma in the fresh state is curved and somewhat resembles a bow, hence its name. It is a crescent body with tapering ends, measures about 6 by 1.5 microns and shows only one constant internal structure, the nucleus. The parasites may be either intracytoplasmic or extracellular. When intracytoplasmic they are massed together and often appear smaller and ovoid. Intracellular collections vary considerably in size, may reach 50 microns in length and are then easily visible with low magnification. Reproduction takes place by binary longitudinal fission. At one time multiple division (schizogony) was also thought to occur, but this observation has not been confirmed and was apparently due to misinterpretation of the intracellular masses.

In addition to its presence in man, Toxoplasma has been reported in a great variety of animals, including, and this is suggestive, those frequently in contact

with man, that is, domesticated or semidomesticated animals or pets, such as dogs, rabbits, mice, rats and birds.

Are the infections in man and in animals caused by one or more species of *Toxoplasma*? All the evidence thus far produced indicates that there is only one species. This conclusion has been reached since (1) toxoplasmas originating from any one animal are infective for many generically different hosts, and (2) Toxoplasmas of different origins cross immunize against each other.

Since *Toxoplasma* has such a wide distribution among animals, it is not surprising that it is equally widely distributed geographically, now having been reported from all continents. Cases of human infection have now been reported from Czechoslovakia, Netherlands and Brazil and, in the United States, from Boston, New York, Chicago and St. Louis.

Concerning transmission information is not yet complete. It has been proved that congenital transmission takes place both in man and in animals. It is likewise proved that carnivorous animals may acquire the infection by ingestion. These are the only two methods established and do not appear adequate to explain all the cases: notably, those of adult infection in man and of toxoplasmosis in herbivorous animals. It has been suggested that arthropods, notably ticks, may transmit the disease, but experimental support for this view has thus far not been obtained.

The diagnosis may be suggested by the clinical data which Dr. Crothers has so ably presented in connection with the disease in infants. In adults the symptoms appear to be less well defined; neurologic manifestations are not conspicuous, and abnormalities of the heart, lungs and liver may furnish the outstanding signs.

Of the laboratory procedures which are available for diagnosis, direct demonstration of the parasite has an unusually high value. Toxoplasmas have been seen in sediment from the spinal fluid and in the papules which sometimes occur as a cutaneous manifestation of the disease; in case of the latter biopsy may be considered. At autopsy the lesions are usually conspicuous, and parasites are seen within or at the periphery of these cutaneous areas. In the congenital type the tissues which are most often invaded are the brain and eyes, and in the noninfantile type, the lungs, heart and liver.

Indirect means of demonstration involve animal inoculation and serologic tests. The intracerebral inoculation of mice is the preferred method. Blood, spinal fluid, ground tissue—all may produce infection, which results in death usually in one to three weeks, but the animals should not be discarded for two months. One inadequacy of this method is the frequency of spontaneous infection in mice. Therefore it is advisable to use numerous animals—at least six, which are chosen if possible from different litters. Guinea pigs and rabbits may also be used, subject to the same caution, and may be more susceptible to certain strains than mice.

Embryonated chicken eggs can also be infected. For diagnosis they have one certain advantage; i. e., they are not known to have spontaneous toxoplasmosis. They are, however, less sensitive to small doses of the infecting organism than are mice when inoculated as described in the preceding paragraph.

Several serologic tests have been described, but only one has been used in connection with human cases. This is a protection test in which two sets of progressive dilutions of the living toxoplasma material are prepared. One set is mixed with the serum to be tested; equal amounts of normal serum or of Tyrode's solution are added to the other set, which serves as the control. A single rabbit is inoculated intracutaneously with both sets of infective material. Results are read at the end of ten to twelve days. The control inoculations result in areas of necrosis, which vary roughly with the infective dose inoculated; protection is manifested by a smaller area of necrosis as compared with that for an equal infective control dose. The value of this reaction is being established. It is probable that a negative result will prove to be of little value in excluding toxoplasmosis, whereas a positive reaction is significant, although the degree of specificity is not yet known.

The pathologic lesions are conspicuous and important. They consist of multiple foci of necrosis of variable extent infiltrated with polymorphonuclear and mono-

nuclear leukocytes and plasma cells. Lesions of this type are most frequent in the central nervous system, meninges and eye or in the heart, liver and lung. Some of the lesions of the brain become calcified and are then visible ante mortem with roentgen rays.

Difficulties in the differential diagnosis of the parasite in the tissues arise with five groups of parasites: *Trypanosoma cruzi*, *Leishmania*, *Histoplasma*, *Sarcocystis* and *Encephalitozoon*. The distinction may usually be made on morphologic grounds alone, although cultures and animal inoculations furnish additional criteria.

DR. BRONSON CROTHERS: The disease has, of course, been described by Dr. Wolf and Dr. Sabin and their colleagues. The clinical material I report is chiefly interesting because the children are older than those in many reported cases. It has been my experience that the suggestion of toxoplasmosis should arise when the ophthalmologist is puzzled by the presence of choreoretinitis. If calcification of the brain occurs in addition the presumption is strong. Treatment after cerebral or ocular invasion is presumably futile, but the fact that the mother may react positively suggests that efforts at treatment, in the attempt to prevent infection of future children, should be made.

DR. CLEMENS E. BENDA, Wrentham, Mass.: When I saw Dr. Crothers' roentgenograms and heard his discussion of the calcification, I thought of tuberous sclerosis. Of course the two diseases are entirely different, but it struck me as significant that Dr. Crothers described lesions in the heart, the liver and the lungs, together with the calcifications in the brain. In cases which have been considered instances of tuberous sclerosis lesions in the heart and liver have frequently been shown—especially the rhabdomyoma of the heart is frequently associated with tuberous sclerosis. I wonder whether some of the cases in which the diagnosis has previously been tuberous sclerosis were not really cases of toxoplasmosis. I should like to ask whether in Dr. Crothers' cases the skin was sometimes affected, and what kind of cutaneous changes were observed.

DR. BRONSON CROTHERS: I think Dr. Weinman has found definite evidence at times of lesions of the skin.

DR. DAVID WEINMAN: Yes. I have not as yet studied the lesions in tuberous sclerosis.

DR. PAUL I. YAKOVLEV, Waverley, Mass.: How were the cutaneous lesions distributed?

DR. DAVID H. WEINMAN: They were disseminated in the 2 cases I recall. In 1 case small pinkish, very firm papules were observed. In another case the lesions were reddish pink and suggested typhus. Also, they were not distributed in any particular region of the body.

DR. PAUL I. YAKOVLEV, Waverley, Mass.: It is evident that tuberous sclerosis and cerebromeningeal angiomas, or Weber-Sturge disease, on one hand, and toxoplasmic encephalitis, on the other, are entirely different conditions. Nevertheless, one may readily see how easily the confusion may arise, and it is quite likely that the diseases will be confused at times. Indeed, clinical features, such as the mental deficiency, the epileptic fits, the occurrence in siblings and the strikingly similar appearance of intracerebral calcifications in roentgenograms, are common to these conditions. Histopathologically, the confusion is hardly possible. Indeed, as has been seen today, the toxoplasmic encephalitis is an infectious, inflammatory and degenerative disease in which a pathogenic agent is often demonstrable. Nothing of the sort is ever seen in cases of tuberous sclerosis or cerebromeningeal angiomas. The difference between these two "neoplastic malformations," which they essentially are, and the toxoplasmic encephalitis is of about the same magnitude as the difference between a neoplasm or malformation and a necrotizing inflammation. There are clinical differences, too, that should permit differentiation in most cases. First, the calcification in tuberous sclerosis and in cerebromeningeal angiomas does not seem ever to occur before puberty; second, these two conditions are system diseases which involve not only the nervous system but, in a characteristic fashion, the skin and

other structures of ectodermal derivation, such as the retina, the nails and the visceral ganglia and plexus. In the presence of such systemic generalization of the neoplastic malformations, the confusion with toxoplasmic encephalitis should not be possible. I must admit, however, that in cases without neurocutaneous manifestations, the differentiation between these malformations and the toxoplasmic encephalitis may present considerable difficulty.

DR. ALEXANDRA ADLER: What is the character of the spinal fluid in toxoplasmosis?

DR. BRONSON CROTHERS: I have had only 1 case in the acute stage, that of a baby, and in that the disease was, I should think, of two or three months' duration. There was no sign of actual activity at that time, and nothing abnormal was noted in the spinal fluid. In some of Wolf's cases there have been a high protein content and indiscriminate signs of inflammation of the eyes. Dr. Wolf says the organism was seen in the sediment in 1 clinical case.

Book Reviews

Unconsciousness. By James Grier Miller. Price \$3. Pp. 329. New York: John Wiley & Sons, 1942.

The author is to be complimented especially on two things—he has written the book in good style so that it is readable and pleasing; second, he meticulously defines his terms and never lets the reader forget the sinfulness of ambiguity. In this one senses the influence of Lawrence Henderson, who struggled so valiantly to bring the exactness of chemistry to the aid of sociology.

There are two objectives in this monograph. The first is to show that much harm has come from the divorce of academic and laboratory psychology from clinical psychiatry. The second is the discussion of unconsciousness.

"Consciousness is a central problem for both the psychological laboratory and the psychiatric clinic, for academic psychologists, psychoanalysts, and psychiatrists alike. There has, however, been little cooperation between them in investigating it. It is essential that a *rapprochement* between the various psychological sciences be accomplished. The issue of unconsciousness offers an excellent occasion to illustrate how this can be achieved. It is only one of many problems in which all branches of the psychological science will find mutual benefit in cooperation. Such a coordinated program is the procedure offering the greatest hope that, in the future, sense can be made in many fields of human personality and behavior which today are realms of ignorance and nonsense.

"The enigma of unconsciousness has been studied and disputed by psychologists for many years. It has been approached from many angles, from the neurological at the one extreme to the philosophical at the other. It has been the subject of careful experimentation on the one hand and of soaring theorizing on the other. The problem has embraced such different phenomena as fainting, hypnosis, inattention, creativity, repression, and instinctual behavior.

"Some who have interested themselves in these questions have seen that all these sorts of unconsciousness cannot be identical, and they have often insisted that they do not even have similar characteristics. Therefore, various terms have been invented, compounds of the word conscious, in order to distinguish and explain these different phenomena. Such words as 'subconscious,' 'preconscious,' 'foreconscious,' 'superconscious,' 'coconscious,' and so forth. The result of this neologizing, however, has not been increased clarity, but greater confusion. Moreover, many dissimilar sorts of behavior are still called 'unconscious' without any effort's being made to define the various senses of this wide term.

"This book attempts to distinguish the various meanings of the word 'unconscious' which have been used, and to describe and differentiate carefully the diverse sorts of human behavior which have been included under this term. Then each of the phenomena is considered at length; the clinically and experimentally determined facts about each one are reviewed; and an evaluation is made of the present state of knowledge on that specific subject. Not until this detailed study of each sort of unconsciousness has been made can the common aspects of them all be thrown into their proper light in a way that is even slightly more than speculative. When such a procedure is followed, however, solid bases for a tentative theory of unconsciousness begin to appear. Only by such an approach can any conclusion be reached as to how conscious behavior is like unconscious and how it is different."

Unconsciousness is discussed and described in the senses commonly in use; there are so many that the word practically loses its usefulness as a medium to convey scientific ideas. The author not only shows this but brings in a wealth of

interesting material, critically evaluated, concerning such subjects as amnesia, volition, insight, attention, suppression and repression. The book is well documented and will repay careful reading by those interested in this central theme of psychology and neurology. It will please no reader who rides a hobby and thinks he already knows the answer.

Conceptual Thinking in Schizophrenia. By Eugenia Hanfmann and Jacob Kasanin. Nervous and Mental Disease Monographs, No. 67. Price \$2.50. Pp. 115. New York: Nervous and Mental Disease Publishing Company, 1942.

In the study reported in this monograph, the authors set themselves the task of testing Vigotsky's theory that conceptual thinking suffers impairment in schizophrenic patients. Vigotsky's concept formation test was used. In this test, blocks of various shapes, sizes and colors are presented to the subject, who is expected to sort them into four groups by discovering what combination of characteristics is indicated by nonsense words written on the backs. The subjects tested comprised 62 schizophrenic patients, 24 patients with organic disease of the brain (dementia paralytica and arteriosclerosis) and 95 normal controls. In analyzing the performance of each subject, the authors recognized three major phases: (1) the interpretation of the instructions; (2) the attempts at solution, and (3) the finding and mastering of the correct solution. In each of these phases of performance three levels of performance were distinguished: (1) the extremely primitive, "concrete" performance; (2) a performance in which certain aspects of conceptual thinking were present and others absent, and (3) the performance based on fully developed conceptual thinking. A quantitative method is presented for evaluating the performance of each subject in terms of these levels.

The results obtained by this method of analysis of the subjects' performance are reported in detail. Several of them seem of particular interest. For instance, a close relationship was noted between performance at the highest conceptual level and high educational level. To this reviewer, the authors seem, at this point, to overlook the opportunity for clarifying the basic question as to whether this relationship is not actually one between intelligence level and high performance. Even among the normal subjects only the college-educated group performed on the highest conceptual level, the noncollege normal subjects performing at the intermediate level. Among the college-educated schizophrenic subjects a wide variation of performance was found, one-third showing superior conceptual performance and another third a primitive performance that fell far below the average even of the uneducated normal subjects. The schizophrenic group was sorted out on the basis of various clinical syndromes and the level of performance determined for each group. Unimpaired conceptual thinking was found most frequently in the group of patients characterized by prevalence of neurotic symptoms, while impairment was most evident in the groups showing (1) disturbance of intellectual function expressed in a tendency to incoherence and irrelevance, (2) marked dissociation with extensive fantastic elaboration of ideas and (3) a paranoid-hebephrenic trend with dull affectivity. While these observations seem to indicate that impairment in conceptual thinking is not, as Vigotsky claimed, the central disturbance in schizophrenic thinking, although it may be found in cases in which the personality is grossly affected, the authors formulate their conclusions rather confusingly by stating that their study "confirms" Vigotsky's thesis that conceptual thinking suffers impairment in schizophrenia. They take issue with Vigotsky's dichotomy of conceptual and "primitive" thinking, which they regard as inadequate, but do not comment on the factor of "regression," which he stresses.

Observations on the schizophrenic subjects and the patients with organic disease are compared, but the differences are less convincing.

The final chapter is devoted to a discussion of the authors' findings in the light of other studies on thinking recorded in the literature.

This study is provocative and stimulating and represents an interesting contribution to the literature of schizophrenic thinking. There is a list of references of sixty-one titles and an index.

The Biologic Fundamentals of Radiation Therapy. By Friedrich Ellinger. Price \$5. Pp. 360, with illustrations. Amsterdam: Elsevier Publishing Co. (New York: Nordemann Publishing Company, Inc.), 1941.

The book is divided into five parts. The first is devoted to a discussion of the action of roentgen rays and the gamma radiation of radium on the various tissues of the body. In many instances the dose of radiation that produces a reversible or an irreversible reaction in the tissues is given. In the second part are described the corpuscular rays and their effect on the body. In the third part ultraviolet light and its action, both direct and indirect, are discussed. Among the direct effects, to name but a few, sunburn and the bactericidal and antirachitic action of the rays are discussed, while among the indirect effects the action of the light on metabolism, respiration, circulation, the blood and the endocrine glands and its use in the treatment of tuberculosis are discussed. In the fourth part of the book attention is given to such subjects as the action of visible light, infra-red rays, the intensification of the action of light and diseases caused by light. The last, or fifth, part of the monograph is concerned with the theories of the effects of radiation, radiosensitivity, the time factor and the general principles for the application and dosage of radiation in therapy. There is a valuable bibliography of 1,100 articles. The author and subject indexes are excellent.

The author is conservative in the presentation of his subject matter. The book is an excellent one and contains an immense amount of accurate and valuable information for the radiologist and for the student. It is a book that every one who is interested in radiation therapy should own.

EXPERIMENTAL STUDIES ON HEADACHE

ANALYSIS OF THE HEADACHE ASSOCIATED WITH CHANGES IN INTRACRANIAL PRESSURE

E. CHARLES KUNKLE, M.D.

BRONSON S. RAY, M.D.

AND

HAROLD G. WOLFF, M.D.

NEW YORK

The relation of intracranial pressure to headache has long been a subject of interest, but the available experimental data are limited. The experimental approach to the immediate effect of drainage of cerebrospinal fluid as a headache mechanism has been made by only a few investigators.¹ In contrast, the headache which so often follows routine lumbar puncture has been studied by many. Such headache has been ascribed by a minority to increased,² and by most to decreased, intracranial pressure.³

Read at the Sixty-Seventh Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 11, 1941.

From the New York Hospital and the Departments of Medicine, Surgery and Psychiatry, Cornell University Medical College.

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(Footnotes continued on next page)

The mechanism of the other common headache often linked with altered intracranial pressure, that occurring with tumor of the brain, has had less attention. As Northfield⁴ emphasized, a necessary relation between the headache and the increased intracranial pressure has been proved.

With these issues in the foreground, the purposes of this investigation were as follows:

- I. To ascertain the mechanism of headache following experimental drainage of cerebrospinal fluid.
- II. To ascertain the mechanism of headache following lumbar puncture.
- III. To ascertain the role of intracranial pressure in the headache associated with increased intracranial pressure.

I. HEADACHE FOLLOWING EXPERIMENTAL DRAINAGE OF CEREBROSPINAL FLUID

A. CEREBROSPINAL HYDRODYNAMICS

When the human subject is in a horizontal position the lumbar, the cisternal and presumably the intracranial (vertex) pressure are

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equal and approximately 50 to 180 mm. of water, but when the subject is erect these pressures diverge. Because the intracraniospinal cavity is not a completely rigid tube, the lumbar pressure then rises to between 375 and 550 mm., which brings the top of the fluid in the manometer near or slightly below the level of the cisterna magna.⁵ The cisternal pressure when the subject is in the erect position rests at a low level, noted to be slightly negative in dogs⁶ and human beings⁷ and measured by one observer as +40 to -85 in man.^{5a} It was suggested by Fremont-Smith and Kubie^{7b} that in the erect human subject the "intracranial" pressure is -150 to -300 mm. The depression noted over the open fontanel in infants who are placed in the erect position supports this contention.

Studies of venous pressure have shown that with postural shift changes occur which parallel those in the cerebrospinal fluid. Weed and Hughson⁸ demonstrated that the intracranial cerebrospinal fluid pressure in animals is slightly greater than the venous pressure as measured in the sagittal sinus. In human beings, also, Myerson and Loman⁹ showed that with the subject in the horizontal position the lumbar pressure is slightly greater than the jugular pressure, and that with tilting of the body head up to an angle of 45 degrees the lumbar pressure rises to between 200 and 270 mm., whereas the jugular pressure falls to zero or lower; reverse changes occur when the patient is tilted head downward. Von Storch and co-workers^{5b} correlated such changes in the venous and the cerebrospinal fluid pressure, postulating that in the erect subject the rise in lumbar fluid pressure represents the transmission via distended intraspinal veins of the hydrostatic effect of the column of blood in the venous channels up to the level of the auricles. Since bilateral jugular compression led to as great an increment in lumbar pressure when the subject was erect as when he was horizontal,

5. (a) Loman, J.: Components of Cerebrospinal Fluid Pressure as Affected by Changes in Posture, *Arch. Neurol. & Psychiat.* **31**:679 (March) 1934. (b) von Storch, T. J. C.; Carmichael, E. A., and Banks, T. E.: Factors Producing Lumbar Cerebrospinal Fluid Pressure in Man in the Erect Posture, *ibid.* **38**:1158 (Dec.) 1937. (c) Loman, Myerson and Goldman.^{1d}

6. Duane, W.; Lewis, R. M., and Ravdin, I. S.: Cerebrospinal Fluid Pressure During Alterations in Posture, *Arch. Neurol. & Psychiat.* **24**:1291 (Dec.) 1930.

7. (a) Ayer, J. B.: Cerebrospinal Fluid Pressure from the Clinical Point of View, *A. Research Nerv. & Ment. Dis., Proc.* (1924) **4**:159, 1926. (b) Fremont-Smith, F., and Kubie, L. S.: Relation of Vascular Hydrostatic Pressure and Osmotic Pressure to the Cerebrospinal Fluid Pressure, *ibid.* (1927) **8**:104, 1929.

8. Weed, L. H., and Hughson, W.: Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by Intravenous Injection of Solutions of Various Concentrations, *Am. J. Physiol.* **58**:101, 1921.

9. Myerson, A., and Loman, J.: Internal Jugular Venous Pressure in Man, *Arch. Neurol. & Psychiat.* **27**:836 (April) 1932.

they asserted that the state of filling of the intracranial veins is unaffected by the change in posture. Working with model systems and animals, Pollock and Boshes¹⁰ reached similar conclusions.

The essential relationship between the venous and the cerebrospinal fluid pressure within the cranium has been summarized by Weed and Flexner¹¹ as follows:

The pressure-equilibrium between cerebral veins and the cerebrospinal fluid [is] that of an elastic membrane separating two fluids which are normally under almost identical pressures but which can exist under very different pressures.

Alteration in the size of the dural envelope with postural shifts has been suggested as another factor in cerebrospinal dynamics.¹² There is no direct evidence concerning the extent of such change. The *dura* appears to be well cushioned and protected from collapse, except perhaps where it underlies the atlanto-occipital membrane and where it surrounds the vessels and nerves emerging from the skull or the spinal column.

From these several data the following formulation seems tenable. In adjustments made to changes in posture, the cerebrospinal fluid pressure follows closely the venous pressure as measured at the same level in the intracraniospinal system. When the human subject is erect, both the venous and the cerebrospinal fluid pressure within the cranium fall to negative values, while the lumbar pressure rises. The height of the rise in lumbar pressure will depend on the height of the venous column above the lumbar sac, that is, on the length of the subject. The zero point lies usually a little above the auricles of the heart and below the cisterna magna. During postural changes the state of distention of intracranial veins is essentially unaltered, for the equilibrium between intravascular and extravascular pressure is maintained.

This balanced relation between the venous and the cerebrospinal fluid pressure in the cranium in spite of changes in position may be diagramed, as in figure 1. For simplification, the slight excess of intracranial cerebrospinal fluid pressure over venous pressure is here waived.

A method by which intracranial pressure can be estimated is illustrated in simplified form by a model of the cerebrospinal fluid system (fig. 2). Like its analogue in man, it represents a compromise between a completely closed and a completely open system. A rubber dia-

10. Pollock, L. J., and Boshes, B.: Cerebrospinal Fluid Pressure, *Arch. Neurol. & Psychiat.* **36**:931 (Nov.) 1936.

11. Weed, L. H., and Flexner, L. B.: Relations of the Intracranial Pressures, *Am. J. Physiol.* **105**:266, 1933.

12. Weed, L. H.: Experimental Studies of Intracranial Pressure, *A. Research Nerv. & Ment. Dis., Proc.* (1927) **8**:25, 1929.

phragm, arbitrarily placed at the top, represents the distensible elements, venous and meningeal, in the human subject. In the typical situation shown in figure 2A, when the model was erect, the total

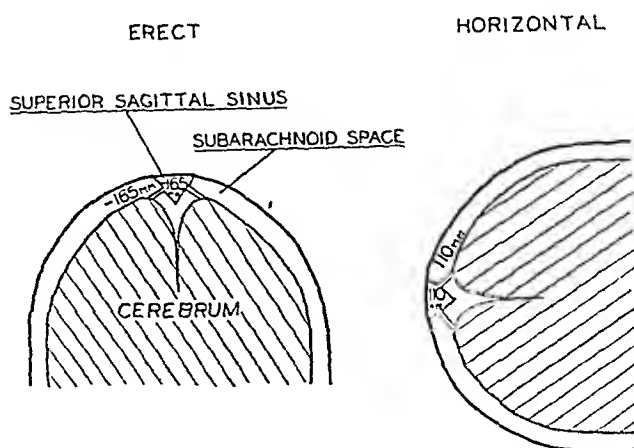


Fig. 1.—Representative normal values for intracranial venous and cerebrospinal fluid pressures in man in the erect and in the horizontal position, illustrating that the balance between the intravascular and the extravascular pressure is probably little affected by change in position. The venous pressures are estimates derived from published measurements of sagittal sinus pressures in animals and jugular venous pressures in man.

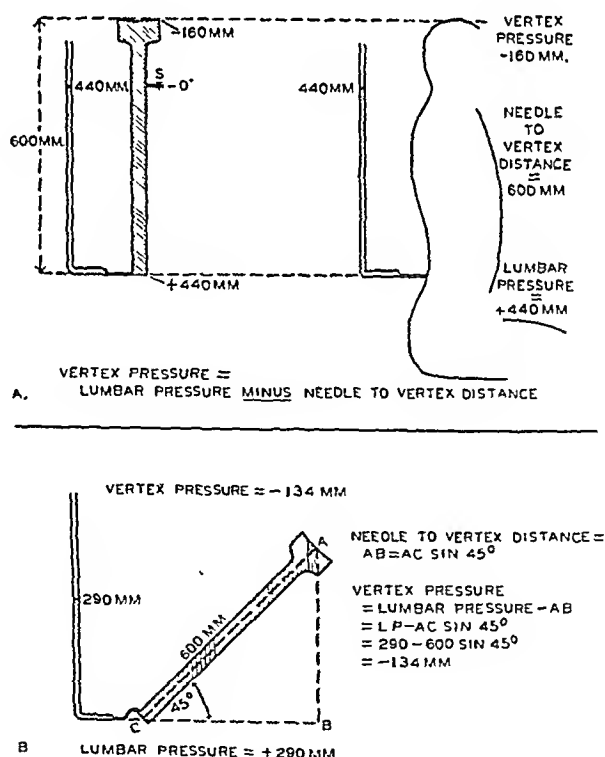


Fig. 2.—Simplified model of the cerebrospinal fluid system, illustrating the method of calculation of intracranial pressure at the vertex in man. A, for the subject in the erect position; B, for the subject in the tilted position.

height of the fluid column was 600 mm.; yet the "lumbar" pressure was 440 mm. The point on the same horizontal level as the meniscus

in the manometer, representing in man a point a little below the cisterna magna, must have a pressure of zero. This was confirmed in the model by opening the stopcock at *S*; there was then neither entrance of air nor escape of fluid. And, finally, the "intracranial" pressure at the vertex must be negative, and to a degree equal to its vertical height above the zero point, or -160 mm. The pressure at the vertex of the model by actual measurement was found to be identical with the calculated value. In short, in this model and in the human subject, the vertex pressure is equal to the lumbar pressure minus the distance from needle to vertex.

When the model was tilted, the vertical distance from needle to vertex was calculated in terms of the angle of tilt, which could readily be measured. It is clear from figure 2 *B* that $AB = AC \times \sin \text{angle}$, and that therefore in the instance shown, with the lumbar pressure 290 mm., the vertex pressure equals the lumbar pressure $-AB$, or $290 - 600 \sin 45 \text{ degrees}$, or -134 mm. In the human subject similar deductions concerning vertex pressure should be possible provided the lumbar pressure, the angle of tilt and the distance between the lumbar needle and the vertex are known.

B. METHOD

Spinal manometric studies were carried out on 11 adult human subjects. Five were females and 6 were males. All were between the ages of 18 and 60 years. In none was there disease of the brain, cord or meninges which could conceivably complicate the interpretation of the experimental results. Lumbar pressure with the subject in the horizontal position was always normal (45 to 150 mm.). In most of the experiments the subject lay on his left side on a specially constructed tilt table, with his thighs flexed in sitting posture and his head supported in the midline of the body. Lumbar puncture was performed between the third and the fourth lumbar vertebra in the usual manner with the use of anesthesia induced with 1 per cent procaine hydrochloride. A no. 19 needle and a 1 mm. glass manometer were used. Observations were made on cerebrospinal fluid pressures at the lumbar sac at various angles of tilt before and after headache had been induced by free drainage of measured amounts of cerebrospinal fluid. The distance from needle to vertex and the angle of tilt were measured directly. The vertex pressure, taken as representative of the intracranial pressure, was calculated as described in the preceding section.

In the experiments in which controlled elevation of intracranial pressure was desired, a flask of physiologic solution of sodium chloride was connected by a rubber tube to the lumbar needle. The fluid level

of the flask, first placed on a level with the needle before the rubber tube was unclamped, was then raised slowly to various measured heights.

Preliminary in vitro tests with the apparatus demonstrated that the lumbar puncture needle was capable of transmitting the fluid quickly in the range of pressures encountered. For example, at 200 mm. pressure, 10 cc. of fluid was delivered through the needle in forty-two seconds, and at 800 mm., in eighteen seconds. Moreover, the assumption that these changes in pressure were rapidly transmitted from the lumbar to the intracranial spaces seems justified by the experiences reported with headache induced by histamine.¹³ In subjects with such temporary headache, elevation of intracranial pressure by this technic caused cessation of the headache beginning in fifteen to ninety seconds. Rapid transmission of pressure changes from the lumbar sac to the cranium has been shown also in cadavers.¹⁴

The 1 mm. glass water manometer was considered sufficiently accurate for this study, for it has been shown that pressures measured with this instrument do not vary greatly from those obtained with a bubble manometer, in which no dislocation of fluid occurs.¹⁵ Within the pressure range handled in these experiments the quantities of fluid entering the manometer were insignificant. As confirmed by measurement, 0.28 cc. was equivalent to each 100 mm. on the manometer scale. Pollock and Boshes¹⁰ noted that as the limits of pressure change of the intracraniospinal system are approached, the addition or removal of small amounts of fluid may be accompanied by large changes in pressure, but in our experiments this was not a point at issue.¹⁰

Another potential source of error, leakage of fluid around the needle from the subarachnoid to the epidural space, was observed occasionally by Ferris¹⁶ in an extensive study of cerebrospinal hydrodynamics. This may have occurred in our studies. But such leakage was probably small, for the lumbar pressures were not high. Moreover, although inferences concerning the amounts of fluid removed must be qualified because of the possibility of hidden leakage, the observations regarding pressures are unaffected by such a possibility.

The pressure readings were, however, complicated by inevitable variations in the degree of relaxation of the subjects, variations which

13. Schumacher, G. A., and Wolff, H. G.: Experimental Studies on Headache: Contrast of Histamine Headache with Headache of Migraine and That Associated with Hypertension, *Arch. Neurol. & Psychiat.* **45**:199 (Feb.) 1941.

14. Masserman, J. G., and Schaller, W. F.: Intracranial Hydrodynamics: Experiments on Human Cadavers, *Arch. Neurol. & Psychiat.* **29**:1222 (June) 1933.

15. Weed, L. H.; Flexner, L. B., and Clark, J. H.: Effect of Dislocation of Cerebrospinal Fluid upon Its Pressure, *Am. J. Physiol.* **100**:246, 1932.

16. Ferris, E. B.: Objective Measurement of Relative Intracranial Blood Flow in Man, *Arch. Neurol. & Psychiat.* **46**:377 (Sept.) 1941.

were reduced as far as possible by reassurance and by attention to postural comfort. To minimize the factors that arose from the subject's reaction to the situation, the measuring apparatus was placed out of his range of vision. The subject was made aware of the general nature of the experiment but was isolated as far as possible from knowledge of when each of the various steps in the manometric studies was undertaken. It should be stated, also, that because of possible inaccuracies in linear and angle measurements, the calculated figures for intracranial (vertex) pressures must be considered as only crude estimates of the actual pressures.

*Manometric Data on the Cerebrospinal Fluid of Eleven Subjects**

Subject	L. P., Horizontal Position, Mm.	L. P., Erect Position, Mm.	N-V Distance, Mm.	V. P., Erect Position, Mm.	Headache V. P., Mm.	Volume, Cc.
F. G.	70	500	630	-130	-280	19
G. F.	70	445	600	-155	-240	15
H. S.	125	490	620	-130	-230	18
E. W.	45	425	590	-165	-215	10
W. O.	80	475	670	-195	-330	19
K. O.	125	...	650	...	-250	18
M. H.	60	...	630	...	-250	15
L. J.	..	460	590	-130	-220	19
S. J.	..	610	640	- 80	-140	c.18
J. D.	..	510	650	-140	-270	17
A. M.	..	425	630	-205	-320	24

* L. P. indicates the initial lumbar pressure; V. P., the estimated initial vertex pressure; N-V, the distance between lumbar needle and vertex; headache V. P., the vertex pressure at which drainage headache first was noted, and volume, the quantity of cerebrospinal fluid drained before headache was noted.

C. RESULTS

1. INDUCTION OF HEADACHE IN ERECT SUBJECTS BY DRAINAGE OF CEREBROSPINAL FLUID.

Observations.—With the subject erect, headache was regularly induced in 11 subjects by free drainage of approximately 20 cc. of cerebrospinal fluid. The calculated vertex pressure, initially between -130 and -205 mm. in all but 1 subject, fell progressively as the fluid was removed, and when the drainage headache¹⁷ first was noted was between -200 and -290 mm. The data are summarized in the table.

The headache when first induced was described as of the vertex or frontal type by all but 1 subject, in whom it was occipital. After fur-

17. For the sake of brevity the headache experimentally induced in this way will be referred to hereafter as "drainage headache." The headache which sometimes is a delayed sequela of routine diagnostic lumbar puncture will be termed "postpuncture headache."

ther drainage the headache not only always increased in severity but usually spread to involve most of the head. It was dull and deep and was not throbbing. In several subjects it was accompanied by sweating, pallor and nausea. Its intensity was sharply increased by shaking of the head, either in a rotary or in a backward and forward direction.

For purposes of analysis, the intensity of the pain was described by the subject on an arbitrary scale of 1 to 10 plus. A typical response is presented in figure 3. In this instance (subject G.F.) drainage of 15 cc. of fluid induced a fall of vertex pressure from —155 to —240 mm., slight bifrontal headache being noted at the latter pressure.

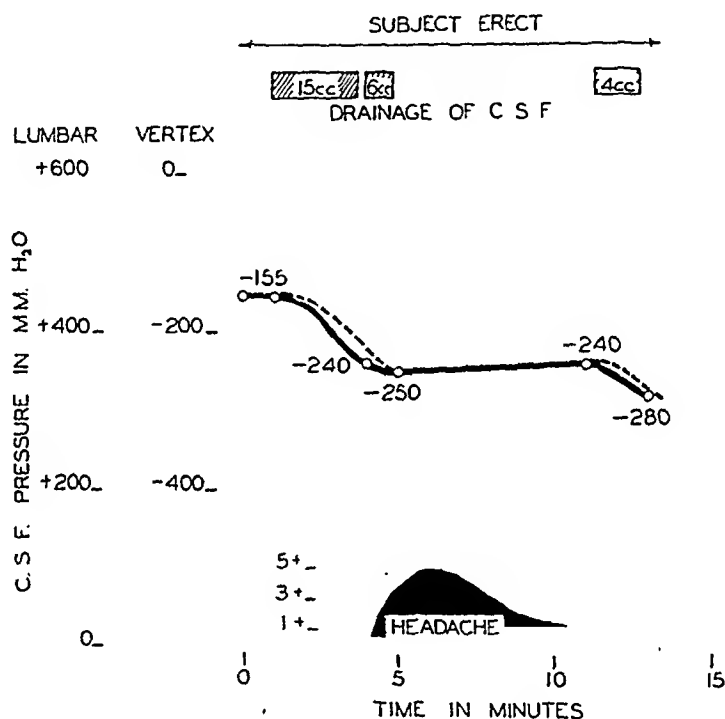


Fig. 3.—Induction of headache with subject in the erect position by drainage of cerebrospinal fluid. The intensity of the headache was described by the subject on a scale of 1 to 10 plus. Slight bifrontal headache was first noted after 15 cc. of fluid had been removed and became moderately severe after the removal of an additional 6 cc.

In this figure and in figures 4, 6, 8, 11, 12 and 13 the lumbar pressure is indicated by a solid black line and the estimated vertex pressure by a broken line.

Comment.—Most of this group of adults responded in a similar way to this test procedure. In general the more negative vertex pressures obtained when the subject was in the erect position were found in the taller persons, i. e., those with the longer needle-vertex distances. In most subjects the vertex pressures at which drainage headache was first noted were similar. The quantities of fluid removed before headache occurred were predictable. They represented approximately 10 per cent of the estimated total volume of cerebrospinal fluid.^{3a}

2. ELIMINATION OF DRAINAGE HEADACHE BY RESTORATION OF CEREBROSPINAL FLUID VOLUME.

Observations.—In 4 subjects in the erect position, after headache had been induced by drainage of cerebrospinal fluid, physiologic solution of sodium chloride was injected intrathecally by the technic outlined in a previous section. When the pressure was raised to the initial level of lumbar pressure or higher, the headache in each case progressively diminished, being completely eliminated in two to four minutes. The lag in reduction of headache was shortened by elevation of the pressure to abnormally high levels, as illustrated in figure 4. In the subject (G.F.) in the experiment illustrated in this graph drainage was

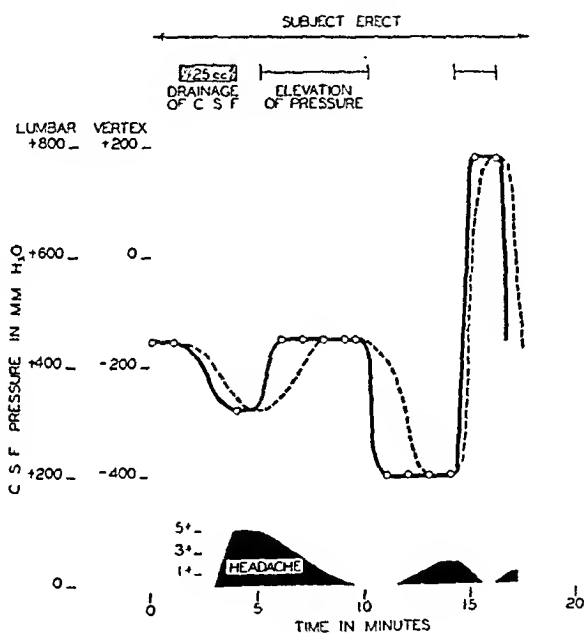


Fig. 4.—Elimination of drainage headache by intrathecal injection of saline solution. Under measured pressure, with the subject erect, physiologic solution of sodium chloride was injected through the lumbar needle during the two intervals shown.

continued until 25 cc. was released and headache of moderately severe degree was present. The introduction of physiologic solution of sodium chloride, raising the pressure to the previous normal level of 445 mm. (lumbar) and —155 mm. (vertex), eliminated the headache in three and a half minutes. On a second trial, elevation of the pressure to a high level of 780 mm. (lumbar) and 180 mm. (vertex) eliminated a milder headache in one minute.

Comment.—The short delay in reduction of intensity of the headache when the pressure was returned to normal probably resulted from a lag in transmission of the added fluid to the intracranial cavity. Apart

from this delay, drainage headache can be varied in intensity in a predictable way by the removal or the restoration of cerebrospinal fluid.

On the basis of the data thus far presented it is convenient to introduce at this point a hypothesis concerning the mechanism of the headache associated with removal of cerebrospinal fluid. The brain normally exerts traction on the structures which support it within the cranium, and this traction may under certain conditions be augmented enough to cause pain. The argument supporting this statement is as follows:

(a) Within the dura mater the brain lies almost entirely surrounded by cerebrospinal fluid, being thus cushioned against sudden movement and protected from excessive sliding contact with the dura. It is not, however, supported entirely by the medium in which it is immersed, as comparison of the density of the solid and that of the liquid will indicate. Data concerning the density of the human brain are scanty, but Vierordt¹⁸ cited, from two separate sources, figures for the specific gravity as 1.039 and 1.040. The specific gravity of cerebrospinal fluid, more readily obtained, is commonly given as 1.007 to 1.008.¹⁹ In observations on a single specimen of material obtained eight hours post mortem, with a modification of the Hammerschlag technic, we found that the specific gravity of sections of cerebrum and cerebellum was 1.041 at room temperature. A sample of spinal fluid from another subject had a specific gravity of 1.007.

The weight of the normal adult brain varies within moderate limits, but averages 1,300 Gm.²⁰ It may then be derived that a 1,300 Gm. brain with a specific gravity of 1.040 immersed in fluid with specific gravity of 1.008 would have a net weight of 41 Gm. The weight of the spinal cord, about 30 Gm.,²¹ with a specific gravity of 1.030,¹⁸ is relatively so small that it can be disregarded in these considerations. In the example cited here the extra 41 Gm. of brain weight must be supported within the cranium by something more than the buoyant effect of the cerebrospinal fluid. It is probable that this moderate weight is shared by suspension from the vault above and by support from structures at the base below. Suspension from above is probably largely through the cerebral veins tributary to the superior sagittal sinus, with a smaller contribution through the cerebellar veins tributary to the transverse and the straight sinuses. Supporting the brain from

18. Vierordt, H.: *Anatomische, physiologische und physikalische Daten und Tabellen*. Jena, Gustav Fischer. 1906, pp. 59 and 449.

19. Vierordt.¹⁸ Merritt and Fremont-Smith.^{2a}

20. Appel, F. W., and Appel, E. M.: *Intracranial Variation in the Weight of the Human Brain*, *Human Biol.* 14:48, 1942.

21. Gray, H.: *Anatomy of Human Body*, ed. 22, Philadelphia, Lea & Febiger, 1930. p. 749.

below, in addition to the floors of the anterior, middle and posterior fossae, are the tentorium cerebelli and the large vascular structures at the base, chiefly the circle of Willis and its immediate branches. The relative contribution of each of these structures to the support of the brain is entirely conjectural. The relations of some of these structures and the direction of stress when the subject is in the erect position are outlined diagrammatically in figure 5 *A* and *B*.

(*b*) These various anchoring vascular structures have been shown to be sensitive to pain when, on operative exposure, they are stimulated

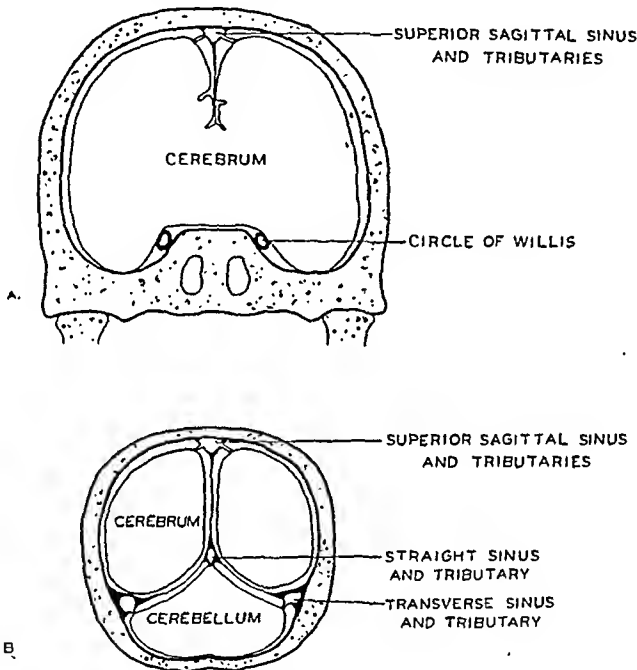


Fig. 5.—Pain-sensitive structures sharing in the support of the brain within the cranium of the subject when in the erect position. *A*, coronal section through the head at the middle fossa, showing the venous tributaries to the superior sagittal sinus and the circle of Willis. The inferior sagittal sinus is omitted because its tributaries are so few. *B*, coronal section through the posterior third of the head, showing the veins tributary to the superior sagittal, straight and transverse sinuses.

by distortion or traction.²² Pain arising from structures on or above the superior surface of the tentorium cerebelli has been shown to be

22. (a) Fay, T.: Mechanism of Headache, *Arch. Neurol. & Psychiat.* **37**:471 (Feb.) 1937. (b) Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance in Headache, *Arch. Surg.* **41**:813 (Oct.) 1940. (c) Penfield, W., and McNaughton, F. L.: Dural Headache and Innervation of Dura Mater, *Arch. Neurol. & Psychiat.* **44**:43 (July) 1940.

transmitted by the fifth cranial nerve and referred to the anterior half of the head. Pain arising from structures on or below the inferior surface of the tentorium cerebelli is transmitted chiefly by the ninth and tenth cranial nerves and the upper three cervical nerves and is referred to the posterior half of the head. Such observations indicate that the basic mechanisms of headache involve traction on these major intracranial vessels or on the cranial and upper cervical nerves which carry pain fibers, as well as dilatation of intracranial arteries or inflammation about any of these pain-sensitive structures of the head.^{22b}

An effective demonstration of the sensitivity to pain of the structures which anchor the brain is provided by the simple device of vigorous head shaking. By either rotary or backward and forward shaking a monetary, but clearcut, headache can be induced in many normal subjects. As was noted previously, the same procedure applied to a subject with drainage headache caused a sharp increase in the intensity of the pain.

(c) The mechanical adjustments which take place within the cranio-vertebral spaces of the erect human subject when cerebrospinal fluid is removed have never fully been analyzed. The problem indeed is not readily accessible to direct study. That some adjustments must occur cannot be denied, and that they are complex is probable.¹²

One basic fact concerning the adjustment is that the lumbar and the intracranial cerebrospinal fluid pressure fall with removal of fluid. Since the intracraniospinal venous pressure is probably essentially unchanged by drainage of fluid, the intravascular and the extravascular pressure are then no longer in balance. Also, since veins are thin walled and, within moderate limits, passively adjust to the pressures within and about them, it may be inferred that dilatation of veins within the cranium and the spinal canal occurs. If the walls of the veins offered no resistance to distention, venous dilatation could completely compensate for a moderate loss of fluid and the intracranial pressure would remain unaltered, but because of their elasticity the compensation is incomplete. Accordingly, the intracranial cerebrospinal fluid pressure slowly falls when fluid is removed. Arterial size is much less dependent on extravascular support than is venous size, and whatever dilatation in the arteries may occur is largely active, rather than passive.²³

Evidence that venous dilatation does occur after drainage of cerebrospinal fluid has been recorded by Forbes and Nason.²⁴ Direct observations through cranial windows in cats revealed that after removal

23. Wolff, H. G.: *The Cerebral Circulation*, *Physiol. Rev.* **16**:545, 1936.

24. Forbes, H. S., and Nason, G. I.: *The Cerebral Circulation: Vascular Responses to (A) Hypertonic Solutions and (B) Withdrawal of Cerebrospinal Fluid*, *Arch. Neurol. & Psychiat.* **34**:533 (Sept.) 1935.

of fluid through the cisterna magna the pial veins and venules dilated moderately, whereas the pial arteries did not. In addition, the bulk of the brain appeared to increase slightly, for its surface approached nearer the window. Confirmation of such venous dilatation and increased bulk came with the further observation by these authors that after the readjustment had occurred, the fluid removed could not be reinjected intrathecally without the pressure's being raised well above its initial level. The latter maneuver has been repeated on human subjects, with similar results.²⁵

(d) Another possible mechanical effect of the removal of cerebrospinal fluid from the subject in the erect position is that such a procedure may directly increase the degree of traction by the brain on the structures which suspend it from above and support it from beneath. There are no data or experimental methods to guide an exploration of this possibility. Yet it may be reasoned that the drainage of fluid from the lumbar sac and the consequent lowering of the intracranial pressure need have no direct effect on the support requirements of the brain. As fluid is removed and the venous bed dilates in partial compensation for the loss, the brain itself probably becomes slightly heavier. But since at the same time it increases in volume, the change in its density is minor, for the additional blood brought to the brain has a specific gravity of 1.060.²⁶ Moreover, although the thickness of the layer of cerebrospinal fluid enveloping the brain may thus become less, the brain must still be virtually completely immersed in the fluid, for the brain case remains a closed box except for the distensible vascular bed. The increase in the "net" weight of the brain following drainage of fluid may thus be so slight as to be insignificant.

When air is introduced to replace lost cerebrospinal fluid, as in the pneumoencephalographic procedure, the situation pictured here is radically different. As fluid is progressively replaced by air, the buoyant support of the brain is diminished; its "net" weight increases from approximately 40 to 1,300 Gm., and traction on anchoring structures is augmented to such a degree that intense pain results. The severe headache induced during pneumoencephalographic examination may in part be explained on this basis.²⁷ However, to repeat, no such series of circumstances follows simple drainage of cerebrospinal fluid.

25. Masserman and Schaller.^{1a} Masserman.^{2a}

26. Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 374.

27. Elsberg, C. A., and Southerland, R. W.: *Headache Produced by Injection of Air for Encephalography*, *Bull. Neurol. Inst. New York* 3:519, 1934. Brewer, E. D.: *Etiology of Headache, Occurrence and Significance of Headache During Ventriculography*, *ibid.* 6:12, 1937. von Storch, T. J. C.; Secunda, L., and Krinsky, C. M.: *Production and Localization of Headache with Subarachnoid and Ventricular Air*, *Arch. Neurol. & Psychiat.* 43:326 (Feb.) 1940.

This analysis indicates that the downward sag of the brain probably is not strikingly altered by drainage of moderate amounts of cerebrospinal fluid. Yet the presumptive increase in brain volume following drainage may itself effect increased traction on anchoring structures, and in a manner distinct from the downward sag of the brain due to gravity. Merely because of the expansion of the brain, the veins which course obliquely over the convexities to join the large sinuses may be subjected to an augmented tug. Also, painful displacement of the vascular structures at the base may similarly result.

Hence, two potential factors in the production of drainage headache have become apparent in the preceding discussion: 1. Granted that intracranial venous dilatation follows removal of cerebrospinal fluid, it may be inferred that such dilatation may cause pain, at least in those veins which in the erect subject are already under constant longitudinal traction by the brain mass. In other words, distention of an anchoring vein joined with lengthwise pull by the brain may distort the wall of the vein to such a degree that headache results. 2. The increase in brain volume secondary to extensive venous dilatation may conceivably produce such distortion of anchoring structures above and at the base that headache is produced.

In recapitulation, then, it is suggested that a fall in intracranial pressure following the removal of cerebrospinal fluid in the erect human subject leads both to intracranial venous dilatation and to an increase in the usually mild and painless traction by the brain on its anchoring structures. With regard to the veins over the top of the cerebrum and cerebellum anchoring these to the superior sagittal, straight and transverse sinuses, the two factors may act in combination. Drainage headache may thus be considered to be traction headache, with traction on dilated veins of primary importance.

It is to be noted that the absolute level of intracranial pressure is not an essential consideration in such a hypothesis. Although the experiments thus far described with the subject in the erect position appear to indicate a rigidly direct relation of drainage headache to lowered intracranial pressure, changes in position of the subject on the tilt table and the application of jugular compression demonstrated effects which qualified this relationship. The results, as reported in the following sections, support the concept of a traction mechanism of drainage headache previously outlined. It is evident that if the subject is tilted after drainage headache has been induced, the vertex pressure can be raised to the "normal" for the subject in the erect position. At the same time, (1) the intracranial venous pressure can be raised and the balance between the intravascular and the extravascular pres-

sure varied, and (2) such traction by the brain as may exist under the influence of gravity can be altered both in direction and in degree. In this way the two factors in our thesis, venous dilatation and traction by the brain, can be dissociated from lowered intracranial pressure per se. The analyses follow later.

3. LACK OF DEPENDENCE OF DRAINAGE HEADACHE ON LOWERED INTRACRANIAL PRESSURE.

Observations.—If the subject was tilted from the erect position, drainage headache could be induced at a vertex pressure less negative than that which occurred normally when the subject was erect and free from headache. As shown in figure 6, when the subject (E.W.) was erect, the calculated vertex pressure was -165 mm. With drainage,

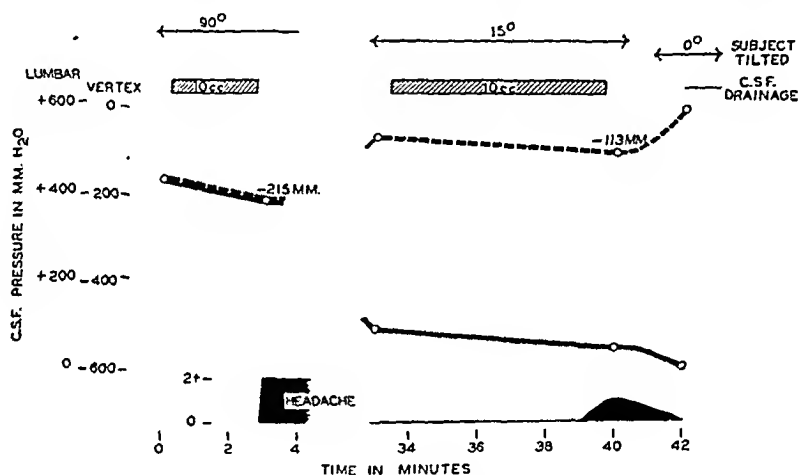


Fig. 6.—Drainage headache induced in subject in the tilted position at a vertex pressure less negative than that which was normal when the subject was erect and free from headache. The graph demonstrates that drainage headache is independent of the absolute level of vertex pressure. There was no headache at a vertex pressure of -165 mm. when the subject was erect at the onset of the experiment. When the patient was tilted at an angle of 15 degrees to the horizontal (thirty-eight minutes later) headache was induced by drainage at a vertex pressure of -113 mm.

bifrontal headache began at a vertex pressure of -215 mm. After further drainage, tilting to an angle of 15 degrees to the horizontal eliminated the headache. Then the further removal of 10 cc. of fluid induced headache again, this time at a vertex pressure of only -113 mm. In 2 other subjects (M.H. and H.S.) similar results were obtained.

Comment.—In the experiment cited, the subject was symptom free when erect, with a normal vertex pressure of -165 mm. Yet after

fluid was removed and the patient tilted to an angle of 15 degrees to the horizontal, headache occurred with a vertex pressure somewhat higher, i. e., —113 mm. The estimated intracranial venous pressure with the patient at this angle of tilt was approximately zero. It may be inferred, therefore, that the intracranial veins dilated to such a degree that even though the downward traction sag of the brain was partly relieved by the tilting, the distortion of the anchoring veins was sufficient to produce pain. The degree of headache bore no direct relation to the absolute level of intracranial pressure. The postulated relations between headache and intracranial mechanics in this subject are illustrated in simplified form in figure 7. The diagrams emphasize the effect which removal of cerebrospinal fluid probably has in altering the normal balance between the pressure inside and that outside the intra-

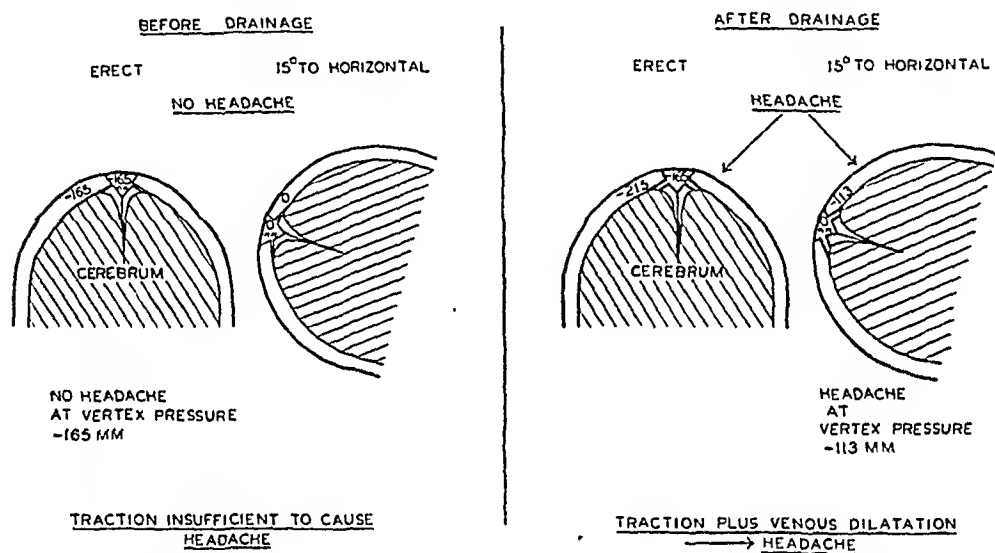


Fig. 7.—Diagram of venous dilatation as part of mechanism of drainage headache, with reference to the results of the experiment shown in figure 6. Distention of the pain-sensitive veins tributary to the superior sagittal sinus (or straight or transverse sinuses) follows drainage of fluid. This augments the traction on these veins by the brain, which they partly support, and leads to headache. For the purpose of simplification, the effect of an increase in brain bulk as a second factor in increasing the traction is omitted from consideration here.

cranial veins. To aid in the clarity of the diagrams, increase in brain bulk secondary to drainage, a second factor in augmenting traction on anchoring structures, is omitted from consideration.

In another experiment, the relative lack of dependence of drainage headache on intracranial pressure was shown in a different way. When the patient was tilted, drainage headache was almost eliminated at a vertex pressure even more negative than that at which moderate headache had been present when the subject was erect.

Observation.—As shown in figure 8, after drainage when the subject (H. S.) was erect, headache began at a vertex pressure of -230 mm. Later, after more fluid was removed and the subject was tilted to an angle of 40 degrees to the horizontal, the vertex pressure was -235 mm. and shortly thereafter -248 mm.; yet the headache was almost eliminated.

Comment.—It may be assumed that as this subject was tilted the diminution of downward traction by the brain thus effected was sufficient to reduce the pain stimulus. Even though the intracranial veins undoubtedly remained dilated, the sag on them in this instance became so slight that the headache was reduced in intensity.

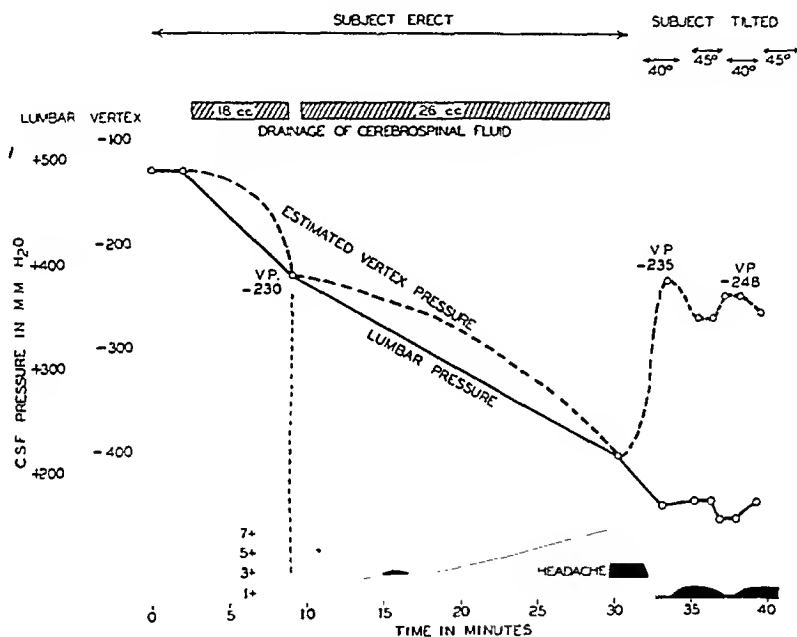


Fig. 8.—Drainage headache reduced in intensity at a vertex pressure more negative than that at which moderate headache had been present when subject was erect. In contrast to the experiment illustrated in figure 6, in which drainage headache was induced even though the vertex pressure was higher than normal here, by tilting the subject, drainage headache was decreased in intensity in spite of a fall in vertex pressure subsequent to further drainage. This result, again, demonstrates that headache of this type is independent of the absolute level of vertex pressure.

4. PROMPT RESPONSE OF DRAINAGE HEADACHE TO SMALL CHANGES IN ANGLE OF TILT AND INTRACRANIAL PRESSURE.

Observations.—In 4 subjects it was found that the intensity of the drainage headache changed relatively rapidly in response to small changes in angle of tilt and in pressure. In the instance in which this was most clearly evident, headache induced by drainage while the subject (H. S.)

was erect was rapidly reduced by tilting him to an angle of 40 degrees, whereas it recurred when the angle of tilt was 45 degrees, the corresponding vertex pressures being -235 and -270 mm. With repeated shifts between these two positions the headache came and went in predictable sequence, the time lag being less than thirty seconds.

Comment.—These results are consistent with a mechanical origin of drainage headache. In the experiment cited it is probable that the direction and degree of traction by the brain, and perhaps also the degree of distention of anchoring veins, rested at a "critical" level. Under these conditions headache could be made to come or go with slight alterations in traction.

5. INCREASE IN INTENSITY OF DRAINAGE HEADACHE DURING JUGULAR COMPRESSION.

Observations.—In a total of 5 trials on 4 subjects (H. S., S. J., A. M. and J. D.) drainage headache was moderately increased in intensity during bilateral jugular compression for ten to fifteen seconds. In each trial the cerebrospinal fluid pressure rose between 22 and 110 mm. The headache, frontal in type, was increased moderately without change in location.

In 1 subject (K. O.) jugular compression for ten seconds caused bifrontal and occipital drainage headache of moderate degree to be eliminated completely for one and a half minutes. During the compression the vertex pressure rose 130 mm. to reach -250 mm. A sixth subject (W. O.) noted no change in headache during or after jugular compression for twenty-five seconds, with a 160 mm. rise in vertex pressure to reach -160 mm.

Comment.—That intracranial veins are distended by jugular compression is well known and is the basis of the Queckenstedt test. The increase in drainage headache usually accompanying this procedure undoubtedly represents the effect of additional distortion of pain-sensitive anchoring veins, which are already dilated and under traction by the brain. The arteries are not affected by jugular compression, since the increase in intracranial venous pressure is not transmitted back to the arterial tree. Moreover, it will be recalled that jugular compression actually reduces the intensity of the headache induced by arterial dilatation after intravenous injection of histamine.²⁸

28. (a) Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. 1:907, 1939. (b) Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Histamine Headache, A. Research Nerv. & Ment. Dis., Proc. (1934) 15:417, 1935.

It is of additional interest that the increase in drainage headache induced by jugular compression occurred in spite of a rise in estimated intracranial pressure to the normal range. This is further evidence that intracranial pressure per se has little to do with drainage headache.

6. REDUCTION IN INTENSITY OF DRAINAGE HEADACHE BY FLEXION OR EXTENSION OF HEAD.

Observations.—In 3 subjects with drainage headache in the erect position, the effect of acute flexion or overextension of the head was noted. Flexion of the head (brow down) or extension (brow up) was carried to such a point that the plane of the occiput, normally vertical, became horizontal. In 2 of the subjects the maneuver completely eliminated the headache during the one minute period of flexion or extension of the head; in the third subject the intensity of the headache was considerably reduced. When the head was flexed or overextended, the lumbar pressure rose 15 to 80 mm. In addition to this increment, the vertex pressure was increased even more because flexion or overextension of the head shortened the vertical distance between lumbar needle and vertex. In 1 subject, for example, flexion of the head caused the lumbar pressure to increase from 325 to 370 mm. and the estimated vertex pressure to rise from —345 to —140 mm., while the headache was almost completely eliminated.

Comment.—These observations, similar to data obtained by McNaughton on patients with postpuncture headache,²⁹ permit no additional inferences concerning the mechanism of drainage headache. Since a significant rise in intracranial pressure inevitably accompanied the changes in position of the head, it cannot be inferred that the relief of headache represented solely a change in the direction and degree of the sag of the brain on its supports.

7. AFFERENT PATHWAYS FOR DRAINAGE HEADACHE IN A SUBJECT WITH PREVIOUS SECTION OF THE LEFT TRIGEMINAL, GLOSSOPHARYNGEAL AND UPPER FOUR CERVICAL NERVES.

Observation.—In addition to the data obtained on the 11 normal subjects, opportunity presented itself to study drainage headache in an adult female (G. C.) who had previously had section of the roots of the fifth and ninth cranial nerves and the upper four cervical nerves, all on the left side, for anomalous "neuralgic" head pains. As a result of the operative procedures she had analgesia over the entire surface of the left side of the head, buccal cavity and nasopharynx except for a small area of the concha of the ear and on the posterior wall of the bony

29. McNaughton, F. L.: Personal communication to the authors.

portion of the external auditory canal. At the time of the experiment she was experiencing a headache of moderate intensity in the right frontotemporal, the vertex and the bioccipital region, which had been present almost constantly for the previous nine months. Removal of cerebrospinal fluid with the subject erect led to increase in her headache, but there was no headache in the left frontal region of the head (fig. 9).

Comment.—As is usually true of histamine headache in subjects with section of the trigeminal root,³⁰ drainage headache spared that area of the head which has been shown to depend largely or entirely on the fifth cranial nerve for its sensory innervation. The head pain in the left posterior region in this subject was probably mediated via the left tenth cranial nerve, which, with the ninth cranial and the upper cervical nerves, shares in pain referred to this area.

This experiment indicates that the fifth cranial nerve on each side is the principal afferent pathway for that part of the pain of drainage headache located over the front half of the head.

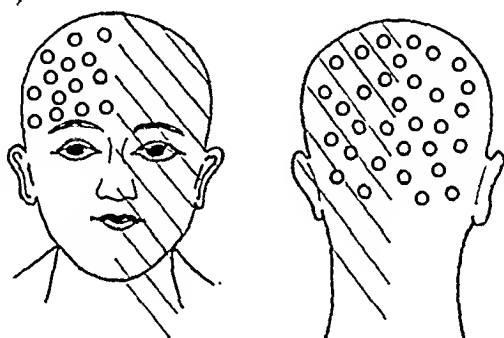


Fig. 9.—Drainage headache in a subject with previous section of the roots of the fifth and ninth cranial and the upper four cervical nerves, all on the left side. Areas of drainage headache are indicated by circles and correspond to the distribution of a milder spontaneous headache. Areas of analgesia are indicated by oblique hatching.

D. FORMULATION

In the foregoing paragraphs it has been shown that there is no direct dependence of drainage headache on intracranial pressure. The headache can be produced by drainage of cerebrospinal fluid and eliminated by its restoration. It is postulated that such headache represents traction by the sagging brain on pain-sensitive anchoring structures.

30. Schumacher, G. A.; Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of Histamine Headache and Its Pain Pathways, *Arch. Neurol. & Psychiat.* **44**:701 (Oct.) 1940. Pickering, G. W., and Hess, W.: Observations on Mechanisms of Headache Produced by Histamine, *Clin. Sc.* **1**:77, 1933. Northfield.⁴

Dilatation of anchoring veins and an increase in volume of the brain secondary to loss of cerebrospinal fluid are held to be important factors in augmenting the degree of traction. The association of these several factors in the mechanism of drainage headache is outlined in figure 10. The development of the argument has shown that data obtained by shifts in the angle of tilt and by jugular compression are consistent with this hypothesis.

E. CONSIDERATION OF OTHER SUGGESTED MECHANISMS

Other explanations of drainage headache merit analysis. Arterial dilatation, mentioned briefly by Pickering,^{28a} is an unlikely cause. Because of the relatively thick walls, the size of arteries is probably little affected by a reduction in extravascular support. Not only is evidence lacking that arterial dilatation accompanies removal of cerebrospinal fluid, but the independence of the headache of the absolute level of intracranial pressure and the prompt response of the headache to tilting or

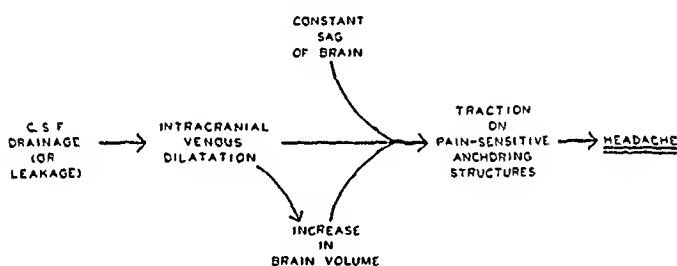


Fig. 10.—Schematic outline of the mechanism of drainage headache. The relevance of this diagram to the consideration of postpuncture headache is discussed in part II.

to jugular compression are inconsistent with this theory. However, it is evident that of all the intracranial arteries, only those of the circle of Willis appear to share in the support of the brain. Displacement of these large vessels may well contribute to drainage headache, but without further evidence their dilatation need not be assumed.

MacRobert³¹ has suggested that with the loss of fluid the brain may sag on the clivus and compress the basilar venous plexus, this displacement raising the intracranial venous pressure and the intracranial pressure. In spite of its stress on the possibility of venous distention, this theory is invalidated by the lack of evidence that a block in the basilar plexus can lead to the chain of events pictured. The basilar veins represent a relatively minor part of the intracranial outflow. It is improbable that their compression would significantly alter intracranial dynamics.

A third possibility is that drainage of fluid may lead to a difference in pressure between the inside and the outside of the third and lateral ventricles. In this event, particularly if the intraventricular pressure should materially exceed that without, traction on the vessels over the convexity of the brain and at the base may occur and a headache analogous to that of internal hydrocephalus be produced.³¹ That such a pressure differential can play a part in drainage headache, except in transient and mild form, seems unlikely, for, as the technic of pneumo-encephalography has demonstrated, the passage of fluids from the intraventricular to the extraventricular spaces is normally freely and rapidly achieved.

II. HEADACHE FOLLOWING LUMBAR PUNCTURE

The headache experimentally induced by drainage of cerebrospinal fluid has its clinical analogue in the headache which so frequently follows diagnostic lumbar puncture. The evidence for this linkage is of two types: First, the reports of many observers indicate that postpuncture headache is associated with loss of cerebrospinal fluid, and, second, studies now to be reported demonstrate the similarity of the responses of drainage and of postpuncture headache to certain experimental procedures.

Postpuncture headache may be defined as the headache, mild or severe, which may appear a few hours to several days after lumbar puncture, lasting a variable period of days or, rarely, weeks. It is a sequel to lumbar puncture in approximately 1 out of every 4 patients.³² The pain is a dull, deep ache and may be throbbing. It is usually bifrontal and often also suboccipital. In the latter position it may be associated with moderate stiffness of the neck. Most characteristic are its occurrence when the subject is erect and its virtual elimination when he is horizontal. Shaking the head makes it more intense. It is usually resistant to all treatment except rest in bed in the horizontal position and the passage of time. Because of the frequency of its occurrence, the occasional severity of the discomfort and the duration of the disability, headache of this type has been of clinical interest ever since the technic of lumbar puncture was introduced.

31. Kunkle, E. C.; Ray, B. S., and Wolff, H. G.: Studies on Headache: The Mechanisms and Significance of Headache Associated with Brain Tumor, *Bull. New York Acad. Med.* **18**:400, 1942. Ray and Wolff.^{22b}

32. Davenport, K. M.: Post-Puncture Reactions, *New York State J. Med.* **39**:1185, 1939. Kulchar, G. V., and King, A. D.: Use of Sodium Amytal in Prevention of Reactions Associated with Lumbar Puncture, *Arch. Neurol. & Psychiat.* **30**:170 (July) 1933. Nelson.^{3b} Perkel.^{3m}

A. RÉSUMÉ OF THE LITERATURE

Although theories concerning postpuncture headache have been clearly contradictory, the weight of the evidence supports the view that it is usually related to a loss of cerebrospinal fluid secondary to leakage through the dural hole. The accumulated data may be summarized as follows:

(a) Postpuncture headache is accompanied by lowered cerebrospinal fluid pressure. Without citing actual data, several observers³³ have reported that in patients with postpuncture headache on whom a second puncture was done the lumbar pressure had fallen from its initial level. The studies of postpuncture headache by Nelson and Jacobeus and Frumerie present pressure data in detail.³⁴ In each of several patients with postpuncture headache the pressure observed on a second tap was low. One of the group reported on by Jacobeus and Frumerie, a patient with severe headache, stiff neck, pallor and bradycardia, had a lumbar pressure of zero. Injection of 90 cc. of physiologic solution of sodium chloride raised the lumbar pressure to 250 mm. and caused immediate clinical improvement, which was maintained by elevation of the foot of the bed. Similar results were obtained with a second patient.

Manometric studies on a group of 16 patients with postpuncture headache were made by Pacifico.^{3d} The interpretation of the results is complicated by the fact that at least 3 of the patients had very high pressures on the initial tap, and 8 of the remaining 13 patients had an unexplained elevation to 210 mm. or above (in the horizontal position). In all but 2 of the group a second puncture twenty-four to ninety-six hours later, and after headache had begun, demonstrated that the pressure, measured in both the erect and the horizontal position, had fallen from the initial levels.

(b) The dural hole at the site of lumbar puncture may persist for several days after the procedure. At laminectomy Mixter noted the presence of a dural hole six days after lumbar puncture, and Castro Silva confirmed this in observations made eight to fifteen days after puncture.³⁵

(c) Leakage of cerebrospinal fluid through the dural hole into the epidural space may occur. Such leakage, first suggested by Sicard as a factor in postpuncture headache, was observed by Pool³⁶ in myeloscopic studies performed two to four days after lumbar puncture, as well as by Ingvar^{3e} in the dissection of cadavers. The latter noted in 1 patient the presence of subcutaneous fluid following lumbar puncture. Moreover, in histologic studies of the repair reaction following dural puncture, he observed that the plug which forms over the hole appears fragile and insecurely fixed.

33. Solomon, H. C.: Effect on Human Cerebrospinal Fluid Pressure of Extraction and Injection of Fluid, *A. Research Nerv. & Ment. Dis., Proc.* (1927) 8:82, 1929. Targowla and Lamache.^{2c} Merritt and Fremont-Smith.^{3a} McNaughton.²⁹

34. Nelson.^{3b} Jacobeus and Frumerie.^{3c}

35. (a) Mixter, W. J., in discussion on Fremont-Smith, F.; Merritt, H. H., and Lennox, W. G.: Relationship Between Water Balance, Spinal Fluid Pressure and Epileptic Convulsions, *Arch. Neurol. & Psychiat.* 28:956 (Oct.) 1932. (b) Castro Silva, cited by Koster, H., and Weintrob, M.: Complications of Spinal Anesthesia, *Am. J. Surg.* 8:1165, 1930.

36. Pool, J. L.: Myeloscopy, *Surgery* 11:169, 1942.

(d) Measures which diminish the likelihood of leakage have been claimed to be effective in reducing the frequency and severity of postpuncture headache. Cisternal rather than lumbar tap, the use of a small needle, the insertion of catgut in the dural hole and the introduction of air into the epidural space to eliminate the hypothetical epidural negative pressure have all been said to be useful devices in the control of postpuncture headache.³⁷ None of these technics, however, is entirely effective. The value of the use of catgut has been shown to be slight.³⁸

(e) Temporary decrease in the intensity of postpuncture headache may result from procedures which increase the volume of cerebrospinal fluid. The intravenous administration of hypotonic solutions (of sodium chloride or distilled water) has been found by several observers to diminish postpuncture headache.³⁹ Conversely, it has been reported that a hypertonic solution of dextrose given intravenously augments the headache.⁴⁰

The argument that increased cerebrospinal fluid pressure is usually related to postpuncture headache is not well founded. The relevant observations are few, and the inferences are of dubious validity.⁴⁰ As will be discussed later, however, the probability exists that in a few patients with postpuncture headache an unusual headache mechanism may be involved, accompanied by but not dependent on elevated pressure.

B. OBSERVATIONS ON POSTPUNCTURE HEADACHE

Various studies to be described under appropriate sections were made one to five days after lumbar tap on 9 patients with typical postpuncture headache. In 1 additional subject unusual opportunity was afforded for special observations, which will be reported separately later in this paper. All the subjects were between the ages of 19 and 40 years and were considered to be accurate witnesses. Six were males and 4 were females.

1. POSTPUNCTURE HEADACHE ELIMINATED BY RESTORATION OF CEREBROSPINAL FLUID VOLUME.

Observations.—Manometric studies on a young woman were made during a typical postpuncture headache. After a routine lumbar puncture bifrontotemporal headache had developed, which recurred whenever she sat erect. The headache was augmented during brief bilateral jugular compression. Five days later, when the headache had begun to abate, the lumbar puncture was repeated with the patient on the tilt table. As shown in figure 11, the initial pressure (with the patient horizontal)

37. Nelson.^{3b} Kulchar.^{3f} Greene.^{3g} Heldt and Mohoney.^{3h}

38. Heldt, T. J., and Whitehead, L. S.: Clinical Studies in Post-Lumbar Puncture Headache, *Am. J. Psychiat.* **93**:639, 1936.

39. Solomon.^{3k} Alpers.^{3l} Perkel.^{3m}

40. Labat, G.: *Regional Anesthesia*, ed. 2, Philadelphia, W. B. Saunders Company, 1928, p. 505. Masserman (footnotes 1 b and 2 a). Balduzzi.^{2b} Targowla and Lamache.^{2c} Kennedy.^{2e} Pacifico.^{3d} Mixter.^{35a}

was 110 mm., which was slightly lower than the pressure at the time of the first tap. When she was turned to the erect position the lumbar pressure rose to 425 mm., slight bifrontotemporal headache beginning almost at once. The estimated vertex pressure at this point was -245 mm., well below the normal range; it slowly fell during the following six minutes to reach -290 mm., while the headache became moderately severe and nausea, sweating, giddiness and weakness were noted. The intrathecal injection of saline solution under a high lumbar pressure of 800 mm. and a vertex pressure of 130 mm. caused the headache and its associated symptoms to be completely eliminated within two minutes. The headache and other symptoms then recurred when the lumbar pres-

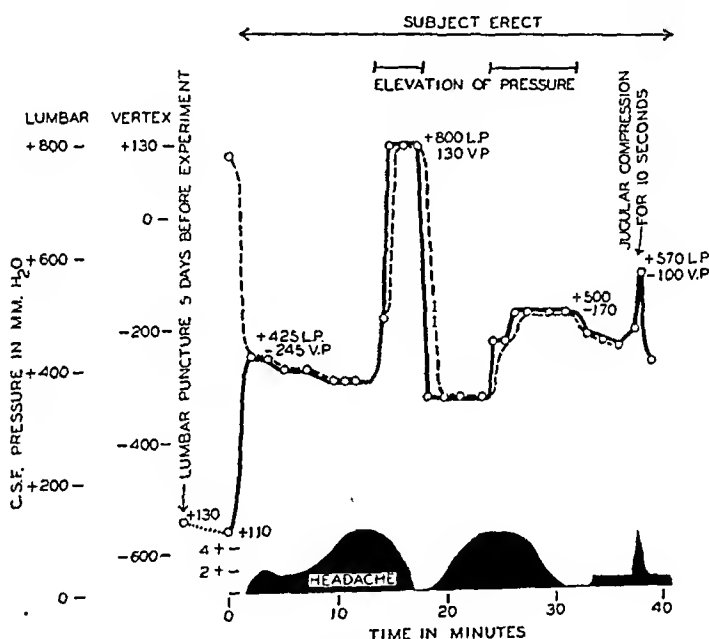


Fig. 11.—Elimination of postpuncture headache by the intrathecal injection of physiologic solution of sodium chloride with subject erect. The experiment was performed five days after the initial lumbar puncture. The response was similar to that noted in the study of drainage headache (fig. 4).

sure was lowered to 350 mm., with a vertex pressure of -320 mm., and were eliminated again in five and a quarter minutes when saline solution was injected and the vertex pressure was raised to a normal level of -170 mm.

Comment.—These results, which parallel the experience of Pickering^{28a} and Jacobsen and Frumerie,^{3c} demonstrate that postpuncture headache, like drainage headache, is reduced by restoration of cerebrospinal fluid volume and that in the erect subject the headache bears a relationship to vertex pressure equally as predictable. Although the lumbar

pressure when the patient was in the horizontal position was only slightly lower than at the time of the first puncture, the pressure was abnormally low when she was turned to the erect position. The reason for the slow fall in pressure during the experiment is not known. It may have resulted from further leakage through the first dural hole.

The direct association of nausea, sweating, giddiness and weakness with the headache suggests that these were manifestations of a response to severe pain rather than merely evidences of anxiety regarding the experimental procedures.

2. POSTPUNCTURE HEADACHE INCREASED BY COMPRESSION OF JUGULAR VEINS.

Observations.—Both jugular veins were firmly compressed manually for ten to fifteen seconds in each of 7 patients with slight to moderate postpuncture headache. The pain was in the bifrontal region in 4 patients, in the bifrontosuboccipital area in 2 patients and in the vertex in 1 patient. In each patient the intensity of the headache was moderately increased during the period of compression. In 2 other subjects jugular compression was carried out a few hours after postpuncture headache had apparently subsided, so that they were able to sit erect at least for short periods without discomfort. In these subjects moderate bifrontal headache was induced by the compression. The headache promptly ended when the pressure was released.

Comment.—As in the observations of Pickering^{28a} and McNaughton,²⁹ the response of postpuncture headache to jugular compression seems definite and predictable. Because a second lumbar puncture could not be done on all these patients, it was not possible to demonstrate that the increase in headache produced by jugular pressure occurred in spite of an associated rise in cerebrospinal fluid pressure. In the single experiment described in the foregoing section and in figure 13, however, manometric studies were possible during jugular compression. As has been shown, repetition of jugular compression caused a definite increase in the headache, even though the estimated vertex pressure rose from —200 to —100 mm. Similar pressure responses undoubtedly occurred in the entire group.

3. POSTPUNCTURE HEADACHE DIMINISHED IN INTENSITY BY FLEXION AND EXTENSION OF THE HEAD.

Observation.—In repetition of studies made by McNaughton,⁴¹ sharp flexion or extension of the head of the single subject on whom this

41. McNaughton, F. L., in discussion on Kunkle, E. C.; Ray, B. S., and Wolff, H. G.: Studies on Headache: An Analysis of Headache Associated with Changes in Intracranial Pressure, Tr. Am. Neurol. A. 67:165, 1941; footnote 29.

maneuver was performed moderately reduced the intensity of postpuncture headache.

Comment.—As was true in the studies on drainage headache, the diminution in the headache here achieved may have been due either to a rise in intracranial pressure or to a change in the direction and degree of the sag of the brain on anchoring structures or to both. At least this much may be inferred: Drainage and postpuncture headache respond similarly to this maneuver.

An attempt to increase intracranial pressure by another technic, the inhalation of amyl nitrite, produced results which are difficult to interpret. In 1 subject, however, postpuncture headache was completely eliminated for four minutes, beginning two and a half minutes after inhalation of amyl nitrite. The relief suggested that dilatation of intracranial arteries is not the basis of postpuncture headache.

GENERAL COMMENT

Without exception, the various procedures adopted in the analysis of postpuncture headache have emphasized its similarity to the headache induced by drainage of cerebrospinal fluid. The two types of headache share the following features: (1) association with decreased intracranial pressure; (2) complete elimination by elevation of the intracranial pressure to normal when the subject is erect; (3) reduction in intensity by change in the subject's position from erect to horizontal or by tilting of the head and (4) increase in intensity by bilateral jugular compression. Accordingly, the headache mechanism outlined in figure 10 may apply both to drainage and to postpuncture headache.

Unlike drainage headache, postpuncture headache may not have its onset until a few hours or days after the lumbar tap. The drainage of the small volume, 5 to 15 cc., of fluid ordinarily removed for diagnostic tests is usually insufficient to cause an immediate headache. The delayed headache presumably is due to the continued slow loss of cerebrospinal fluid after the initial removal of fluid. This type of headache may properly be termed "leakage" headache. Reflex inhibition of choroidal secretion following penetration of the dura has been suggested as the cause of the decreased volume and pressure of cerebrospinal fluid accompanying postpuncture headache,^{2c} but this hypothesis lacks both experimental and clinical support.

It is relevant to note at this point that closure of the dural-arachnoid puncture hole may be aided by inflammatory changes in the meninges and an increase in the cell and the protein content of the spinal fluid such as may be associated with disease of the central nervous system.

This may explain the fact noted by several authors, notably Perkel,^{3m} that in patients with a pathologic fluid headache is less likely to develop after lumbar puncture than in those with a normal fluid. On the other hand, the difference between the two groups may reflect only that patients with normal fluids, as a group being less "ill," may attempt to resume activity sooner after the puncture.

C. ARTERIAL DILATATION ASSOCIATED WITH POSTPUNCTURE HEADACHE

Indirect evidence that arterial dilatation may be concerned in post-puncture headache is suggested by the reports⁴² that the injection of ergotamine tartrate may eliminate the headache.⁴³ The experimental evidence against arterial dilatation as a major factor in drainage headache has been summarized in part I. The same argument applies to post-puncture headache. It appears that dilatation of pial arteries is not responsible for postpuncture headache because such headache is made worse rather than better by firm jugular compression and its accompanying rise in intracranial pressure (in contrast to the response of headache induced by histamine).⁴⁴ Moreover, the pial arteries respond poorly to the vasoconstrictor action of ergotamine.⁴⁵ On the other hand, ergotamine causes definite constriction of the arteries of the dura and

42. (a) Guttman, S. A.: Personal communication to the authors. (b) Targowla and Lamache.^{2c}

43. The effect of ergotamine tartrate on intracranial veins may be small, for the walls of these are thin and have few muscular layers (Wolff, H. G.: *A. Research Nerv. & Ment. Dis., Proc.* [1937] **18**:29, 1939). Yet constriction of retinal and temporal veins following the intravenous injection of ergotamine tartrate has been observed in man (Graham, J. R., and Wolff, H. G.: *A. Research Nerv. & Ment. Dis., Proc.* [1937] **18**:638, 1939). Moreover, it may be noted that in Guttman's experience the doses of ergotamine usually required to alleviate post-puncture headache were larger than those found adequate in the treatment of migraine headache and that repetition of the drug was often required (Guttman.^{42a}). The favorable influence of ergotamine tartrate on postpuncture headache may, therefore, be due to slight constriction in the large anchoring veins over the convexities of the brain. No evidence bearing directly on this problem is available. The rise in jugular and in cerebrospinal fluid pressure induced by intravenous injection of ergotamine tartrate is so slight that it may be waived (Pool, J. L.; von Storch, T. J. C., and Lennox, W. G.: *Effect of Ergotamine Tartrate on Pressure of Cerebrospinal Fluid and Blood During Migraine Headache*, *Arch. Int. Med.* **57**:32 [Jan.] 1936).

44. Pickering.^{28a} Clark, Hough and Wolff.^{28b}

45. Pool, J. L., and Nason, G. I.: *Cerebral Circulation: The Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats*, *Arch. Neurol. & Psychiat.* **33**:276 (Feb.) 1935.

scalp (chiefly the middle meningeal, temporal and occipital arteries); the influence of the drug on the large basal arteries of the circle of Willis remains in doubt.⁴⁶ Dilatation of these arteries, whatever the obscure cause may be, cannot be rejected as a factor in postpuncture headache, but their role seems to be at most only accessory.

D. POSTPUNCTURE HEADACHE OCCASIONALLY DUE TO "MENINGITIS"

The "usual," or "typical," variety of postpuncture headache has been the topic of major concern in this discussion. It must be recognized, however, that in a few instances of postpuncture reaction a syndrome is presented in which factors other than mere loss of cerebrospinal fluid must be involved. In these uncommon cases⁴⁷ the headache may have its onset several hours after the tap, while the patient remains horizontal. The headache is unusually severe and often generalized; stiffness of the neck is prominent, and moderate fever is present. A second puncture on such patients has shown the evidences of sterile "meningitis," with low, normal or slightly elevated pressure and pleocytosis, either polymorphonuclear or lymphocytic. Recovery in the reported cases was uneventful.

An example of this alarming variant of the reactions to lumbar puncture was observed recently at the New York Hospital.

A 41 year old man had had symptoms of widespread disease of the spinal cord for two years, which was diagnosed as "myelitis" of unknown origin. He carried a small amount of iodized poppyseed oil in the lumbar sac as the residuum of studies performed elsewhere eight months before. Our initial diagnostic lumbar tap, with the patient in the horizontal position, showed a pressure of 70 mm.; the lymphocyte count was 12 per cubic millimeter, and the protein measured 75 mg. per hundred cubic centimeters. Within six hours of the tap there developed severe fronto-occipital headache, unaffected by position but accentuated by any motion of the head; his neck became stiff, and his temperature rose to 39 C. (102.2 F.). A second puncture, performed forty-eight hours later, showed a

46. Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, *A. Research Nerv. & Ment. Dis., Proc.* (1937) **18**:638, 1939.

47. Mouzon, J.: De quelques procédés préventifs destinés à éviter les inconvénients de la ponction lombaire, *Presse méd.* **35**:997, 1927. Hurxthal, L. M.: Sterile Meningitis Following Lumbar Puncture, *J. A. M. A.* **100**:1489 (May 13) 1933. Ashworth, H. D.: Nervous Sequelae of Spinal Anesthesia, *Proc. Roy. Soc. Med.* **26**:501, 1933. Spiller, W. G., and Payne, F. L.: Meningitic Symptoms Rapidly Following Lumbar Puncture and Rapidly Disappearing, *J. A. M. A.* **82**:106 (Jan. 12) 1924. Reynolds, K. E., and Wilson, G.: Aseptic Meningitis Following Lumbar Puncture, *ibid.* **102**:1460 (May 5) 1934. Targowla and Lamache.^{2c} Koster and Weintrob.^{35b}

lumbar pressure of 170 mm., a count of 800 lymphocytes and 530 erythrocytes per cubic millimeter and a protein content of 400 mg. per hundred cubic centimeters. The fluid was faintly cloudy and colorless and was sterile when cultured. The reaction subsided in five days.

Comment.—The origin of this meningitic type of postpuncture reaction is obscure. Animal experiments suggest that, like the usual form of reaction, it may result from a leakage of fluid, for Kasahara^{1f} showed that the aspiration of relatively large amounts of cerebrospinal fluid from rabbits regularly causes pleocytosis. In human subjects Masserman^{2a} reported a similar reaction. Whatever the cause of the aseptic "meningitis" may be, it is apparent that the immediate mechanism of the headache is much like that of the headache associated with pyogenic meningitis or subarachnoid hemorrhage, i. e., inflammation of the various pain-sensitive structures within the cranium.^{22b}

E. FORMULATION

The usual form of postpuncture headache is an example of headache resulting from mechanical traction. It is due mainly to dilatation of and traction on pain-sensitive vascular structures. The essential factor in the mechanism is leakage of cerebrospinal fluid through the dural hole left by the needle.

Infrequently, postpuncture headache may be caused by sterile "meningitis," and in this event, also, it may be due primarily to leakage of fluid.

The commonly prescribed routine of rest following lumbar puncture thus has a rational basis, although its value has recently been questioned⁴⁸. There can be little dispute that the use of as small a needle as is consistent with the information sought and the avoidance of multiple insertions are important factors in the prevention of prolonged leakage.

III. HEADACHE ASSOCIATED WITH INCREASED INTRACRANIAL PRESSURE

Experimental and clinical evidence indicates that when headache is associated with increased intracranial pressure the headache is not caused by the increase in pressure.

A. INDUCED ELEVATION OF INTRACRANIAL PRESSURE AND HEADACHE

Observations.—In 4 normal human subjects in the erect position, the intrathecal injection of a sterile physiologic solution of sodium

48. Blanchard, M., and Laigret, J.: L'innocuité complète de la ponction lombaire chez les indigènes du Congo, *Presse méd.* **32**:518, 1924. Blau, A.: Reactions Following Spinal Puncture, *Urol. & Cutan. Rev.* **45**:239, 1941.

chloride was used to raise the lumbar pressure to between 680 and 850 mm. and the vertex pressure to a positive pressure of 60 to 220 mm. These elevations in pressure were maintained for one to two minutes without headache in any instance. In one experiment on a subject in the horizontal position both the lumbar and the vertex pressure were held at 510 mm. for ten minutes (fig. 12). No headache was noted, but in the latter part of the trial period painful tingling in the sacral and leg areas was present.

Comment.—The failure of experimentally induced elevation of intracranial pressure to cause headache confirms recent observations by

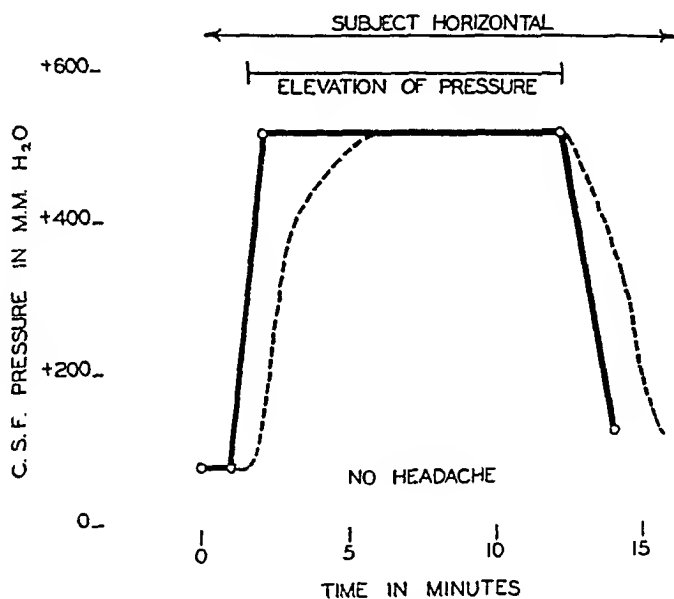


Fig. 12.—Failure of experimentally induced elevation of intracranial pressure to cause headache in a normal subject. With subject in a horizontal position, the lumbar and intracranial pressures were held at 510 mm. for ten minutes without headache.

McNaughton⁴¹ and observations during experimental studies on histamine headache and headache associated with arterial hypertension.¹⁸ In the latter study, intracranial pressures of 800 to 1,000 mm. were produced by intrathecal injection of saline solution but were maintained for only a few moments. Reports by Fay of the production of headache by an apparently similar procedure present a contradiction for which we have no explanation.⁴⁹

49. Fay (footnotes 1 e and 22 a).

B. INTRACRANIAL PRESSURE AND HEADACHE ASSOCIATED WITH TUMOR OF THE BRAIN

In patients with tumor of the brain headache and increased intracranial pressure frequently coexist. As a consequence of the commonly held assumption that such headache must be a direct result of generalized elevation of intracranial pressure, the clinical importance of the headache in the localization of the lesion has been minimized.

It has recently been shown, however, that there is no constant relation between headache due to brain tumor and increased intracranial pressure.³¹ An analysis of 72 patients with tumor of the brain indicated that although the headache may be located at a distance from the tumor, the location of the headache is not fortuitous. The data suggested that headache associated with tumor is produced by traction on intracranial pain-sensitive structures, chiefly the large arteries and veins and the venous sinuses. The traction may affect directly adjacent structures or those at a distance by extensive displacement of the brain. Generalized increase in intracranial pressure is a manifestation of tumor growth and is not essential to the production of tumor headache. Two sets of data confirm this view.

1. FREQUENT ASSOCIATION OF HEADACHE ACCOMPANYING TUMOR OF THE BRAIN AND NORMAL INTRACRANIAL PRESSURE.

Observations.—In the series of 72 patients with tumor of the brain who were studied, headache as a symptom occurred almost as commonly in persons without increased intracranial pressure (19 of 23) as it did in those with increased pressure (46 of 49).³¹ In addition, of the 7 patients who were free from headache, 3 had increased intracranial pressure.

Comment.—These figures, reenforcing Northfield's⁴ observations, demonstrate that increased intracranial pressure is not essential to the production of tumor headache.

2. INDEPENDENCE OF HEADACHE ASSOCIATED WITH BRAIN TUMOR AND INCREASED INTRACRANIAL PRESSURE.

Observation.—The following study was made on a man with a left parietal oligodendroglioma who had had a bifrontal headache for one month, the pain appearing usually when he stood up. At the time of the experiment he was free of headache and was lying horizontally on his left side. The lumbar pressure was 175 mm. As indicated in figure 13, headache, chiefly of the left frontal area, was induced by drainage of 39 cc. of cerebrospinal fluid through the lumbar needle. The headache was then eliminated completely by restoration of fluid and

elevation of pressure to its initial level, the technic of intrathecal injection of saline solution described in part I being employed. Finally, and most significantly, when the lumbar and intracranial pressures were raised to a high level of 550 mm. for five minutes, headache did not recur.

Comment.—The results of this experiment supplement well the evidence already offered that elevation of intracranial pressure in normal subjects fails to cause headache.

GENERAL COMMENT

The thesis which so insistently presents itself when these facts are reviewed, i. e., that tumor headache or other headache is relatively

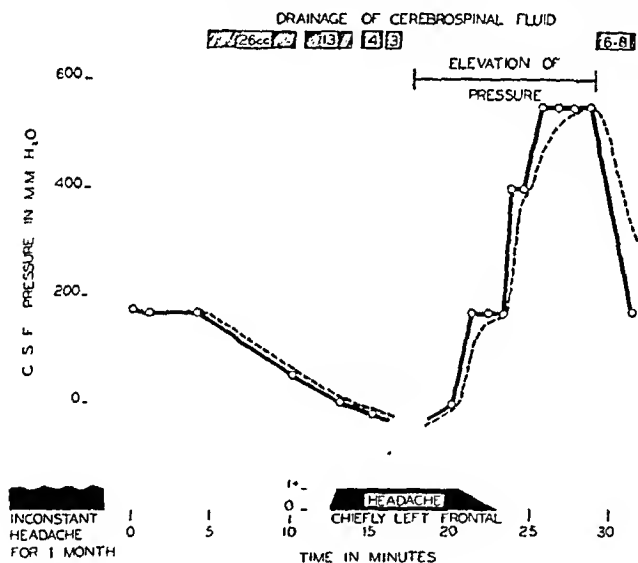


Fig. 13.—Induction of headache by drainage of cerebrospinal fluid and failure of induced elevation of intracranial pressure to 550 mm. to cause headache in a patient with a left parietal oligodendroglioma. The headache following drainage of 39 cc. of fluid was chiefly in the left frontal area. The patient was in the horizontal position and lying on his left side.

independent of increased intracranial pressure, does not of course deny the clinical significance of such elevation of pressure. However, the vital importance of the various effects of rise in pressure is not relevant to this discussion.

The headache associated with meningitis or other types of intracranial infection, in which elevation of cerebrospinal fluid pressure is often noted, is probably similar to headache associated with brain tumor in that it is independent of increased intracranial pressure.^{22b}

SUMMARY AND CONCLUSIONS

Headache was regularly induced in normal erect human subjects by the free drainage of approximately 20 cc. of cerebrospinal fluid, the estimated vertex pressure falling to between —220 and —290 mm. from a normal of approximately —150 mm. Moreover, (a) drainage headache was reduced in intensity by the intrathecal injection of physiologic solution of sodium chloride and the restoration of the cerebrospinal fluid volume; (b) drainage headache was reduced in intensity by tilting the body toward the horizontal or simply by flexion or extension of the head; (c) in its response to postural changes drainage headache was shown to be independent of the estimated intracranial pressure; (d) drainage headache was usually augmented in intensity during distention of intracranial veins secondary to bilateral jugular compression; (e) in a subject who had previously had section of the roots of the fifth and ninth cranial and the upper four cervical nerves, all on one side, induced drainage headache was absent over the homolateral frontotemporal area. This indicates that the afferent impulses from the frontal portion of the area of drainage headache traverse the fifth cranial nerve.

It is thus inferred that drainage headache is caused primarily by traction by the brain on various pain-sensitive structures which anchor it to the cranium; dilatation of some of these structures, the intracranial veins, and increase in brain volume are suggested as joint factors in the *augmented traction which follows drainage of fluid and leads to headache*.

The headache which often follows lumbar puncture has predictable and unique features, all of which indicate its similarity to drainage headache. Like drainage headache, (a) postpuncture headache was associated with a decrease in cerebrospinal fluid volume, as evidenced by a fall in cerebrospinal fluid pressure; (b) it was completely eliminated by the intrathecal injection of saline solution and by the elevation of the intracranial pressure to normal; (c) its intensity was reduced by change from the erect to the horizontal position or by flexion or extension of the head, and (d) its intensity was increased by bilateral jugular compression.

The usual variety of postpuncture headache is therefore similar in type and mechanism to the headache induced by drainage of cerebrospinal fluid; i. e., it is caused by dilatation of and traction on pain-sensitive intracranial vascular structures. It is probably secondary to a prolonged leakage of fluid through the dural hole in the lumbar sac produced by the operator's needle.

Uncommonly, postpuncture headache results from sterile "meningitis."

The headache so often associated with increased intracranial pressure has generally been assumed, but never proved, to be related to the increased pressure. Yet, (a) elevation of intracranial pressure in normal

human subjects to abnormally high levels failed to cause headache; (b) in a series of 72 patients with tumor of the brain, headache occurred almost as frequently with normal as with increased pressure; (c) headache homolateral to the lesion in a patient with a tumor of the brain was induced by lowering the intracranial pressure, but could not be induced by elevation of the pressure to a high level of 550 mm.

Hence, in the production of headache, increased intracranial pressure is neither a prime nor an essential factor.

From these data it is concluded that the headache associated with either decreased or increased intracranial pressure results from traction on or displacement of pain-sensitive intracranial structures and is independent of generalized intracranial pressure changes per se.

Miss Helen Goodell aided in the experiments and the preparation of the illustrations.

925 East Sixty-Eighth Street.

PREDISPOSING FACTORS IN BROMIDE INTOXICATION

ANDRAS ANGYAL, M.D.

WORCESTER, MASS.

With regard to bromide intoxication, opinion is divided as to the relative importance of the direct toxic effects of bromides, on the one hand, and the individual susceptibility and predisposing pathologic conditions, on the other. A recent experimental investigation by Jellinek, Angyal, Cohen and Miller,¹ at the laboratory of applied physiology at Yale University, is of particular interest to this controversy. In that experiment 78 normal subjects received bromides orally for a period of four weeks in high enough doses to produce bromide levels in the blood serum of about 150 mg. per hundred cubic centimeters by the end of the medication period. The outstanding result of this experiment was the paucity of neurologic and psychiatric changes in the subjects when the bromide level in the blood reached values which by many authors have been stated to approach, or even to be within, the toxic zone.

The setting of this experiment was not quite identical with the usual conditions under which bromide psychosis is said to arise. For one thing, it is claimed that bromide intoxication usually—though not invariably—occurs in connection either with a very large intake of bromide in a short time or with a lesser use of the drug over a long period. In the Yale experiments, however, the bromide level in the blood reached a considerable height only during the last week or last two weeks of the experiment and was maintained at this level for only a brief period. It seemed questionable to us, however, whether such factors would explain satisfactorily the difference between the slight changes observed in the experimental subjects and the dramatic delirious picture seen in patients with bromide psychosis. It appeared advisable to inquire whether or not there are any features beyond the presence of bromides in the blood which may be responsible for the psychotic manifestations observed in cases of bromide intoxication.

For this purpose the records of the 21 patients admitted to the Worcester State Hospital during the years 1937 to 1941 with a diag-

From the Worcester State Hospital.

1. Jellinek, E. M.; Angyal, A.; Cohen, L. H., and Miller, D. P.: An Experimental Study of Bromism, *Psychiatric Quart.*, to be published.

nosis of "psychosis due to bromides" were reviewed. This review included only those cases in which the official diagnosis was clearcut. All cases in which the diagnostic label indicated that factors other than bromides were also considered as significantly responsible for the psychosis (e. g., "psychosis due to bromides and barbiturates" or "psychosis due to bromides and alcohol") were excluded. Furthermore, all cases in which the diagnostic impression was first that of bromide intoxication but which subsequently were reclassified under some other diagnostic label were excluded from this study. Briefly, only those cases were used in the present series in which, after sufficient time for observation, the diagnosis of "psychosis due to bromides" was considered by the hospital staff as the most reasonable classification.

It may reasonably be expected that in cases of bromide intoxication some other preexisting condition will almost invariably be found. After all, there must be some personality disturbance—insomnia, restlessness, neurotic disturbances, etc.—responsible for resort to bromides. It was felt, therefore, that only those features which go beyond vague neurotic complaints, or even beyond a distinct neurosis, could be considered as major complicating factors. There was no preconceived notion as to what these factors might be, and hence no specific list of features for which to look in the case records was used.

A study based on the consultation of records rather than on personal examination of patients has certain disadvantages. This is particularly true in a case of such a more or less transient condition as bromide intoxication, in which the patient resides in the hospital for only a short period and in which the case record, particularly the social history, is as a rule less detailed than that of a patient with a condition requiring prolonged psychiatric care. A thorough analysis of personality or a study of subtle deviations of prepsychotic adjustment can therefore not be attempted. Since, however, the purpose of the present study was to determine whether any gross contributing factors were present, the lack of complete information was not a serious handicap.

To anticipate some of the results, in the great majority of cases certain factors were present of which the probable etiologic significance for the psychosis cannot be ignored: cerebral arteriosclerosis, severe alcoholism, organic disease of the brain, involutional complications, etc. Frequently more than one of these conditions was present in a given case. I have roughly classified the cases according to the prevalent complicating factor. In several cases it was doubtful which factor should be given greater weight. This classification is, however, meant to be only a gross grouping to facilitate the discussion.

ARTERIOSCLEROSIS AS A CONTRIBUTING FACTOR

This group comprises 5 cases in which arteriosclerosis—usually associated with heart disease—was considered as the major contributing factor.

CASE 1.—H. J., a married woman aged 59, was admitted to the hospital on March 2, 1938. Three of the patient's 12 siblings died of tuberculosis in their late teens. Anamnestic information was scanty, but no gross abnormality seems to have appeared until about ten years ago. At that time the patient was having the menopause. She began to nag her husband constantly and showed much jealousy. This condition persisted more or less constantly until the present illness. On one occasion she accused her husband of trying to get a waiter in a restaurant to poison her food. During the last three years there had been a marked change in her personality. She became careless in housekeeping and in her personal appearance. She stopped going to church and became rather inactive, spending much time sitting in a chair and not talking to any one. A year ago she compelled her husband to change their residence because she accused him of flirting with the landlady. During the last three or four months her seclusiveness, irritability and suspiciousness increased to such an extent that she had to be admitted to the hospital. The history of the use of bromides was vague. Apparently, she had taken bromides off and on for four or five years preceding her illness, and during the last year had used them at frequent intervals and in increased doses.

On admission she was excited, confused, bewildered and apprehensive and wept frequently. Physical examination revealed that the right pupil was larger than the left; the right pupil did not react to light, and the left responded sluggishly. Abdominal reflexes and the knee and ankle jerks were absent. The blood pressure was 170 systolic and 110 diastolic and dropped later to 160 systolic and 100 diastolic. The retinal vessels were somewhat tortuous and narrowed, and there was evidence of general peripheral arteriosclerosis. The heart was enlarged to the left, and there was slight pitting edema of the ankles. The skin showed an erythematous rash, and numerous red, pinpoint papules occurred over the anterior aspect of the legs and thighs.

One day after admission the bromide content of the blood serum was 100 mg. per hundred cubic centimeters.

By the end of the first week the patient's mental status was much clearer. At the end of the thirty-fifth day period of observation she was well enough to be dismissed from the hospital. Her adjustment, rechecked after one year, was fairly good, but she was rather loquacious and euphoric and showed slight memory defects.

Besides the use of bromides, the following factors may be significant in this case: 1. About the time of the menopause, the patient manifested a mild paranoid condition, which persisted more or less until her present condition developed. 2. Habit deterioration and personality changes had been occurring for three or four years. 3. Advanced arteriosclerosis was present, with which these alterations were consistent. 4. Memory defects persisted long after the effects of bromide were over, and hence it may be presumed that they were present even previous to the episode of bromide intoxication. It is noteworthy, also,

that the psychiatric symptoms were present while the bromides in the blood serum were below what usually is considered a toxic level.

CASE 2.—D. W., a white woman aged 75, was transferred to the Worcester State Hospital on Dec. 7, 1938, after a ten day stay in a general hospital. The past history was scanty and not significant. On admission she was confused and disoriented. She appeared to respond to hallucinations and expressed the belief that her food was poisoned. Physical examination revealed advanced retinal and generalized arteriosclerosis and arteriosclerotic heart disease. The blood pressure was 170 systolic and 110 diastolic. There were no other significant physical signs.

The bromide level of the blood two days after admission was 60 mg. per hundred cubic centimeters. No determinations of the bromide values were made in the general hospital from which the patient was transferred, but presumably the bromide level had been considerably higher. The bromide content dropped slowly; at the end of the fourth week it was still 24 mg. per hundred cubic centimeters. Under treatment with sodium chloride the patient's condition gradually improved, and her confusion, hallucinations and delusions disappeared. She admitted having taken various kinds of medicines for several years, but she could not give any detailed account. After a four month stay in the hospital she was well enough to be discharged to a home arranged by old age assistance.

Advanced arteriosclerosis in a 75 year old woman must be considered as etiologically significant.

CASE 3.—M. R., a woman aged 67, was admitted to the hospital on Oct. 13, 1938. The family and past histories were not remarkable. About two years previous to admission it was noted that the patient began to neglect herself, which was decidedly in contrast to her previous habits. She was also noticed talking to herself as if she were speaking to several persons at a time. A few months previous to admission she began to go to the outpatient department of a general hospital to be treated for iritis, arthritis and hypertension. She complained particularly of vertigo, for which she was given elixir of three bromides (dose not stated). Within a month her behavior became even more peculiar. She wandered about the streets and became forgetful and confused. Occasionally she stopped in front of strange people on the street and speculated in a loud voice what was wrong with them. Several days before admission she stopped eating.

On admission she was drowsy, sleeping day and night and needing to be awakened for feeding. When her drowsiness decreased she appeared depressed, crying easily with no provocation. There was no evidence of hallucinations or delusions. She was disoriented and confused, and her memory was defective.

Physical examination revealed a sluggish pupillary reaction to light and in accommodation, hyperactive tendon reflexes, gross tremor of the fingers, a questionable Hoffmann sign on the left and bilateral knee and ankle clonus, more pronounced on the left. Her speech was thick. The blood pressure was 170 systolic and 80 diastolic, and there was striking peripheral sclerosis. There was a faint systolic murmur at the apex and over the aortic area. She had bilateral nontoxic adenomas of the thyroid. The bromides of the blood serum measured 270 mg. per hundred cubic centimeters one week after admission, 190 mg. four days later and 140, 88 and 44 mg., respectively, per hundred cubic centimeters at successive weekly intervals. With treatment the mental state gradually cleared; in about six weeks there was no evidence of psychosis, and only a moderate degree of memory impairment was the residual defect.

The advanced arteriosclerosis ought to be considered as etiologically highly significant in this case. Habit deterioration, referable to the advanced cerebral arteriosclerosis, was of two years' duration and considerably antedated the use of bromides. It is remarkable, however, that after the signs of bromide poisoning disappeared the patient returned to a state which was apparently better than that which preceded the use of bromides.

CASE 4.—F. T., a white woman aged 65, was transferred from a general hospital on Aug. 3, 1939. The patient's mother died at the age of 50 of carcinoma of the stomach, and one of the patient's daughters died at 40, also of carcinoma of the stomach. The patient was operated on for uterine fibroids, but otherwise she had apparently been well until two years ago, when she began to suffer from attacks of angina pectoris. In 1938 her husband died, and she began to suffer from "nervousness" and insomnia. Without consulting a physician, she began to take bromides (sodium bromide, 2 teaspoonfuls daily) more or less regularly from September 1938 until shortly before her admission to this hospital. In the latter part of July 1939 she refused to eat, became confused and drowsy and staggered when walking. On July 27, 1939 she was admitted to a general hospital. There her illness ran a febrile course, and she was suspected of having a pneumonic process. In the hospital persecutory delusions developed, the patient believing that attempts were being made to poison her. She was then transferred to this hospital. Here she was greatly confused and disoriented and showed defects of memory, but there was no definite evidence of hallucinations or delusions.

Physical examination revealed dehydration, evidence of arteriosclerosis, moderate cardiac enlargement to the right and dulness and rales at the bases of both lungs. The first record of the bromide level of the blood serum, dated two weeks after admission, was 217 mg. per hundred cubic centimeters; a week later it was 54 mg. per hundred cubic centimeters, and after an additional three days, 47 mg. per hundred cubic centimeters.

The patient's condition cleared rapidly, and on the twenty-seventh day after admission she was discharged as recovered from the psychosis.

The arteriosclerotic process seemed to be the chief predisposing factor in this case. It was also important that the patient had had insufficient nourishment and probably an inadequate intake of fluids for some days before admission to the hospital.

CASE 5.—H. H., a white woman aged 66, was transferred from a general hospital to this hospital on July 28, 1941.

Both parents of the patient were said to have suffered from hypertension. The patient had always been nervous and worried constantly. Her past history was otherwise not remarkable. In the last few years she had suffered from headaches and tinnitus associated with hypertension. A month before her admission she had what was said to be a slight shock; she became semistuporous and fell to the floor. There was no paralysis. For a few days she was kept in bed and treated with bromides (amount not stated). Soon she was able to be up and about, but the bromide medication was continued. She became increasingly drowsy, and on July 23, 1941 she was admitted to a general hospital. There she became confused, disturbed and hallucinated and was transferred to this hospital. On admission her speech was slurring. She was resistive, occasionally assaultive,

and confused, fearful and apprehensive. She spoke vaguely of threatening visitations and religious pictures on the wall.

Physical examination revealed the following positive signs: sclerosis of the peripheral vessels, a blood pressure of 196 systolic and 90 diastolic and moderate cardiac enlargement to the left.

The bromide level of the blood serum on the day following admission was 254 mg. per hundred cubic centimeters (bromide content of the spinal fluid 104 mg. per hundred cubic centimeters). The amount of bromide in the blood decreased relatively rapidly, and in thirty-two days the patient was considered recovered from the psychosis.

This seems to be a rather clear case of bromide poisoning superimposed on hypertension and generalized arteriosclerosis.

The 5 patients in this group were all women. Their ages ranged from 59 to 75 years, with an average of 66.4 years. In all 5 patients the physical signs of arteriosclerosis were conspicuous. Two patients presented definite psychotic features before any use of bromides. These features consisted in 1 patient (case 3) of severe habit deterioration and in another (case 1) of a paranoid condition, beginning at the menopause and persisting for about ten years. The second patient also showed habit deterioration of several years' duration. All patients recovered from the immediate toxic effects of the bromides, but the underlying personality disturbances persisted in those patients in whom they were present before the bromide incident. The highest bromide levels in the blood serum recorded for these 5 patients ranged from 60 to 270 mg. per hundred cubic centimeters, with an average of 180 mg. per hundred cubic centimeters.

ALCOHOLISM AS A PREDISPOSING FACTOR

CASE 6.—W. C., a man aged 58, was transferred from a general hospital to this hospital on June 1, 1937. He had been a heavy drinker since the age of 18 years. When intoxicated he was noisy and abusive. On six previous occasions he had been confined in a general hospital with delirium tremens. Seven years ago, for a short period, he was an inmate of the Worcester State Hospital, and at that time his condition was diagnosed as alcoholic psychosis. The patient claimed that for the past year and a half he had not been drinking at all. For the last three years he has been taking daily 2 fluidrachms (7.4 cc.) of a mixture of potassium bromide and chloral hydrate containing 12 grains (0.9 Gm.) of each to the fluidrachm (3.7 cc.). He had increased this amount to 3 or 4 teaspoonfuls daily for a week or two preceding his admission. On May 15, 1937 he again began to drink heavily and became weak and tremulous. On May 21 he became extremely confused and expressed the belief that he had killed some one. On May 27 he was taken to a general hospital, where he became deluded and excited and for that reason was transferred to this hospital.

On admission his gait was staggering and his speech slurred. He was excited and shaky and refused to eat. He stated the belief that people were standing behind him with a gun. He was afraid that he was going to be killed and that the water basins were filled with poison. He was greatly disoriented, and his memory and comprehension were defective.

Physically he appeared poorly nourished and dehydrated, the lips and tongue being crusted. The blood pressure was 160 systolic and 90 diastolic. There was some sclerosis of the peripheral vessels, but the retinal vessels were fairly normal. The liver was enlarged 1 fingerbreadth below the costal margin. The knee jerks were hyperactive.

The bromide level of the blood serum was 109 mg. per hundred cubic centimeters one week after admission, 94 mg. five days and 30 mg. after an additional twelve days. On the twenty-sixth day after admission he was discharged from the hospital. At that time his condition was completely clear.

Catamnestic Note.—Fifteen months later the patient was again admitted to this hospital. The diagnosis at this time was "without psychosis; alcoholism."

It is difficult to state which part of the symptomatology was due to bromides and which part was due to alcohol. The latter factor has to be weighted rather heavily in an etiologic consideration: There were a long history of alcoholism, six admissions to the hospital for delirium tremens, one admission to a mental disease hospital for alcoholic psychosis previous to the episode of bromide intoxication and another admission for alcoholism following this episode. During the two weeks preceding hospitalization there was an increase in the bromide intake, but the alcohol habit was also resumed. Dehydration and malnutrition may also be considered as contributing factors.

CASE 7.—P. O'L., a man aged 39, was transferred from a general hospital to this hospital on Oct. 29, 1938.

The patient's father was alcoholic and died at the age of 33 of tuberculosis. His mother, who was described as "hysterical," suffered from diabetes and hypertension. The patient was the youngest of 6 siblings, 2 of whom died in infancy; the oldest brother died of "alcoholism"; another brother was admitted to this hospital for dementia praecox and died here of pulmonary tuberculosis, and another brother also had tuberculosis as well as a "nervous breakdown" after being graduated from college. The family lived in a very poor environment, and the home situation was extremely chaotic. The patient was described as having been an incorrigible child. He finished the ninth grade, when he was removed from school because of truancy and other behavior problems. He had various jobs, mostly laboring ones, all over the country. He had been a heavy drinker of alcohol since the age of 16, and had a record of more than forty arrests for drunkenness and fifteen arrests for breaking and entering. He had spent six years of his life in jail. On three occasions he was admitted to a general hospital with delirium tremens. In 1924 he became addicted to morphine, taking as much as 30 grains (1.95 Gm.) a day. In 1930 he was taking 14 to 16 grains (0.91 to 1.04 Gm.) of diacetyl morphine and was admitted to a general hospital. After that he became a heavy user of barbitol.

The patient had had one previous admission to this hospital, in 1936. At that time the diagnosis was alcoholic psychosis. On May 15, 1938, after the expiration of one year's trial visit, he was discharged from the hospital. The hospitalization to be discussed took place on October 29 of the same year. The patient stated that just at the time he had previously been discharged from the hospital his mother died and he decided to take drugs again "to forget." He started with $\frac{1}{2}$ grain (0.032 Gm.) of morphine sulfate, increasing the dose until in about five months he was using 15 to 25 grains (0.975 to 1.525 Gm.) daily. He neglected

himself, ate poorly and lost weight. Finally, he voluntarily entered a general hospital on Oct. 1, 1938. Here the dose of morphine was gradually reduced until the patient was not receiving any of the drug. He became restless, agitated and assaultive. In the hospital he was suspected of having drugs smuggled in to him by his friends.

On admission to this hospital he was irritable, suspicious and antagonistic. His speech was slurred and his gait staggering. He had a "picket fence" temperature, which ranged from 90 to 100.6 F., down at night and up in the morning, with an accompanying variation in pulse rate of 45 to 108 per minute. He was extremely nervous, tremulous and agitated. A few days after admission he broke out with what was apparently a bromide rash. Two days after admission the bromide level of the blood serum was 145 mg. per hundred cubic centimeters. Four to six weeks after admission he no longer showed any gross signs of psychosis.

The following factors are relevant for etiologic consideration: (1) possibility of a constitutional weakness because of the patient's extremely poor family stock; (2) psychopathic personality; (3) history of chronic alcoholism, with three incidents of delirium tremens and a previous alcoholic psychosis; (4) addiction to various drugs, and (5) withdrawal of morphine at the onset of the present episode.

CASE 8.—A. W., a woman aged 55, was transferred from the Boston Psychopathic Hospital to this hospital on Dec. 17, 1940. The prepsychotic history was scanty and not remarkable. From puberty she had taken whisky to relieve menstrual pains, but, according to her statement, she did not drink at other times until her father died, in April 1940. Since then she had been drinking excessively. On November 27 she collapsed on the street and was taken to a general hospital in a stuporous condition. There she became unmanageable, and on Dec. 4, 1940 she was transferred to the Boston Psychopathic Hospital. There she was confused, stuporous and disoriented and soon became hallucinated, seeing dogs and elephants, and she expressed the belief that the nurses were going to kill her.

Physically, she appeared dehydrated, and the tongue was covered with crusts of sordes. Gait was unsteady and speech slurred. The reflexes were hyperactive. The heart was slightly enlarged. The bromide levels of the blood serum were 240 mg. per hundred cubic centimeters on December 9, 95 mg. on December 27 and 23 mg. on January 30.

The patient gradually improved, so that on Feb. 20, 1941 she was released on a trial visit. A recheck of her condition six months after her release did not reveal any gross signs of psychosis, but she had many childish ideas and was rather unreasonable.

In this case the etiologic significance of alcohol is somewhat questionable. The postpsychotic residuals (childish behavior and lack of judgment) may be interpreted as indicative of some antecedent deteriorative process which may have predisposed her to the bromide intoxication.

CASE 9.—E. P., a man aged 48, was transferred to this hospital from a general hospital on May 17, 1938. The patient's father died of cancer of the tongue and his mother of cancer of the stomach. Seventeen siblings were dead, all but 3 of whom died in infancy. One brother was in a mental disease hospital, and 1 sister had been "nervous and absent-minded" since the death of her husband.

The patient was a drifting sort of person. He began drinking at the age of 23, and at 25 he was a heavy drinker, doing his drinking alone. He had been arrested six times for intoxication. He had had two attacks of delirium tremens, one ten years and another five years before admission to this hospital, for which he was treated in a general hospital. He had also had a previous admission to the Worcester State Hospital in 1932, with a diagnosis of chronic alcoholism.

Previous to the present admission he had not drunk for about a year. On May 2, 1938 he began to drink again, consuming anywhere from a pint to a quart (475 to 950 cc.) of liquor daily. At the same time he did not eat anything all day. On May 5 he went to a physician, who prescribed for him elixir of three bromides. He bought a 16 ounce (530 cc.) bottle and drank it all within one day. The family noticed that he was talking peculiarly. On May 8 he was taken to a general hospital in a stuporous condition. There he became noisy and threatening and was brought to this hospital on May 17.

On admission he was restless and untidy and required tube feeding. Within three days his condition began to clear up, but there were still much disorientation and confusion and a tendency to confabulation.

His voice was heavy; the pupils were dilated, and the deep tendon reflexes were diminished. He was severely dehydrated. There were rales at the bases of the lungs. A blood count revealed considerable anemia, the red cell count being 3,710,000 and the hemoglobin content 80 per cent. The spinal fluid (on December 25) showed 493 cells per cubic millimeter, with 45 per cent lymphocytes and 55 per cent polymorphonuclear leukocytes. The proteins of the spinal fluid measured 95 mg., the chlorides 742 mg. and the bromides 85 mg. per hundred cubic centimeters. The colloidal gold curve was 0012100000. Because of the changes in the spinal fluid, the possibility of encephalitis was considered. The data available in the case record are insufficient for an accurate diagnosis, but obviously there was present an infectious process involving the central nervous system. The bromide levels of the blood serum were 186 mg. per hundred cubic centimeters on May 20, 180 mg. on May 23, 57 mg. on May 31 and 27 mg. on June 6. On June 18, 1938 the patient was released on a trial visit. By that time he showed no gross evidence of psychosis.

The following factors are etiologically significant: (1) a constitutional weakness, which may be assumed because of the extremely poor family stock; (2) alcoholism, with two incidents of delirium tremens, a previous commitment to a mental disease hospital for chronic alcoholism and excessive consumption of alcohol just preceding the present episode; (3) physical debilitation, with lack of food for days before the onset of the illness and anemia, and (4) infection of the central nervous system.

This group comprised 3 men and 1 woman. Their ages ranged from 39 to 58 years, with an average of 50 years. The past histories of the 3 men of this group were similar. Two of the men had very poor heredity, including the presence of cases of psychosis in the family. All 3 men were chronically alcoholic, with histories of excessive use of alcohol for periods of twenty-three, twenty-five and forty years—long enough to produce organic changes. All had repeated episodes of delirium tremens; all had previous admissions to state hospitals, and 2

of them had had further admissions to a state hospital for alcoholism within a relatively short time after recovering from the bromide intoxication. The history of the woman was quite different from that of the other patients in this group. She apparently had a fairly normal background and had been drinking excessively for only about one year. It is likely, however, that in this case some deteriorative process preceded the bromide intoxication.

All the patients of this group were admitted to the hospital in a state of severe dehydration, a condition which must be considered as etiologically significant. In 1 patient there was present in addition an infectious process of the central nervous system. In another patient phenomena of morphine withdrawal complicated the picture.

The highest readings of the bromide levels of the blood serum ranged from 109 to 240 mg. per hundred cubic centimeters, with an average of 170 mg. per cent.

OTHER DISEASES OF THE CENTRAL NERVOUS SYSTEM AS PREDISPOSING FACTORS

In this group are included 2 patients who showed some organic alterations in the central nervous system other than changes due to alcohol or to an arteriosclerotic process.

CASE 10.—E. H., a woman aged 43, was transferred from a general hospital to this hospital on July 6, 1937. She was well until about a year preceding the hospitalization, when she began to suffer from menorrhagia, which became progressively worse and led finally to entrance to a general hospital on June 18, she being in bed for three weeks preceding hospitalization. She was restless and suffered from insomnia, for the relief of which bromides (dose not stated) were given. Exploration on June 26 revealed large fibroid masses on both sides of the uterus, the one on the right extending to the pelvic brim. Scrapings were not examined microscopically. After an operation the patient became so disturbed that she had to be transferred to this hospital.

On admission she was acutely hallucinated and expressed the belief that the house was on fire and that snakes and other objects were under the bed. She misidentified people and was completely disoriented for time and place. She was extremely restless, with anxiety and apprehension.

Physical examination showed inequality of pupils, with poor reaction to light. There was an apical systolic murmur, which was forced and blowing in character, and the pulse was rapid (102 per minute). Fluid output was low, and the Mosenthal test showed variations in specific gravity of 1,008 to 1017. Gynecologic examination revealed that the uterus was five times the normal size. The diagnostic impression was fibrosis uteri.

The bromide levels of the blood serum were 206 mg. per hundred cubic centimeters on the day of admission, 85 mg. one week later and 58 mg. after an additional two days. The bromides of the spinal fluid were 128 mg. per hundred cubic centimeters on the day of admission and dropped in two weeks to 24 mg. per hundred cubic centimeters.

The patient's condition began to clear after about ten days, and on the fortieth day she was discharged from the hospital as recovered from the psychosis. However, five days after leaving the hospital she became acutely ill with a chill, stiff back and a bilateral Kernig sign. She was taken to a general hospital. Spinal puncture relieved her pain, and she was slightly better. After one week in the hospital, however, she had convulsions for a few minutes, after which she was unconscious, with shallow breathing and extremely rapid pulse. On lumbar puncture the fluid shot out under great pressure. Half an hour after the lumbar puncture she died.

Autopsy revealed acute endocarditis, enlargement of the liver and spleen, uterine fibroids, infarct of the left kidney and acute bilateral pyelitis. The condition of the brain and meninges was as follows: The dura was thickened and firmly adherent to the calvarium; the spinal fluid was bloody. There was a hemorrhagic area over the left frontal region, and the dura was thick and adherent to the surface of the brain. Section in the parietal region, just posterior to the hemorrhagic area, revealed a well organized clot, the size of a small egg, surrounded by an area of softening and necrosis, which was well walled off and did not enter the lateral ventricle. In the posterior portion of the right parietal lobe there was an area of softening 6 by 5 cm., which entered the lateral ventricle. The brain substance in this area was completely absorbed.

Apparently, an acute flare-up of bacterial endocarditis was responsible for the hospitalization of the patient, which took place a week previous to her death. (No blood cultures were made.) The recent cerebral hemorrhage in the left frontal region was apparently a sequela of the endocarditic process. Of greater interest from the present point of view are the extensive lesions on the right and left sides of the posterior portion of the brain. From the autopsy report, it is evident that those lesions must have been present for a considerable period, though they were silent as far as gross clinical manifestations were concerned. Briefly, this case is one in which the bromide acted on an already grossly impaired brain.

CASE 11.—J. S., a man aged 59, was admitted to this hospital on July 20, 1937. The past history was not remarkable. The patient's illness apparently began six months prior to admission, when he complained of chronic tiredness and of not being able to work as well as he used to. He was depressed and discouraged. Three weeks prior to admission he began mumbling unintelligibly and spoke of his being "watched by pictures."

On admission he was confused and unresponsive and had to be fed with a spoon. He was greatly retarded and was almost mute, bringing forth only a few disjointed phrases in a hoarse whisper. When his condition began to clear, he showed pronounced aphasia.

Physical examination revealed moderate general arteriosclerosis. The retinal vessels were sclerosed. There was an acne-like eruption over both upper extremities. Repeated laboratory examinations revealed a consistently positive Hinton reaction of the blood and a negative reaction of the spinal fluid. (The date of the syphilitic infection could not be accurately determined, but, judging from the patient's vague statements, it must have occurred more than twenty-five years

before.) The bromide levels of the blood serum were 103 mg. per hundred cubic centimeters on the day of admission (July 21), 74 mg. on July 27, 53 mg. on August 4 and 0 on August 30. (The duration or the dose of bromide intake was not stated.)

The patient showed gradual improvement. After three months' residence in the hospital he was allowed to go home for short visits. After seven months he was released for a year's trial visit; at the expiration of that period he was discharged from the hospital. Although the acute symptoms did not recur, the patient remained an inactive, irritable, inefficient person in need of supervision.

The acute symptoms occurred with a moderate elevation of the bromide level of the blood. Definite morbid changes probably preceded the use of bromide and remained practically unchanged after the acute episode was over. It is reasonable to assume that the untreated syphilis, of long duration, as well as the arteriosclerotic changes, were highly significant for the production of the clinical picture.

PHYSICAL DEBILITY AS A PREDISPOSING FACTOR

In a number of cases included in the previous three groups there were present debilitating physical conditions, such as insufficient nourishment for a period preceding the psychosis, dehydration and acute infections. To such conditions a certain significance is ascribed as factors predisposing to various organic reaction types. Thus, for example, it has been pointed out by several authors that episodes of delirium tremens are often associated not only with excessive intake of alcohol but frequently with physically debilitating factors, such as exposure to cold, insufficient nourishment, acute infections or occasionally a neglected fracture. A similar consideration may be applicable to bromide psychosis. Though some degree of physical debilitation is more or less the rule in cases of bromide intoxication, in the following 2 cases it can be considered as a major factor.

CASE 12.—C. W., a man aged 44, was admitted to this hospital on April 11, 1937. His father was alcoholic and his mother a rather unstable person. He had been fairly well until recently. In 1936 his wife died, after which he began to drink, but apparently not excessively. The present difficulties began with the following episode. On March 26, 1937 he left his 11 year old daughter in a movie theater, intending to call for her at 10:30 p. m. After having a few drinks, he picked up a prostitute in a tavern. While riding with her in a taxi he was in an automobile accident, sustaining an injury to his leg. He was taken to a hospital, but left against advice, being afraid of a scandal. At home his leg began to swell, and a physician was called. A diagnosis of fracture was made. He was worried about the drinking episode and became restless and sleepless. For relief of this condition he was given bromides (amount not stated). On April 4 he became irrational and excited, and on April 11 he was brought to this hospital.

On admission he was in a deep stupor. When aroused he was confused and disoriented, felt the floor sliding, saw rows of women beside him, saw people bleeding, etc.

Physically he was dehydrated. His right leg was in a cast, with fracture of the internal condyle of the femur. His temperature ranged from 103 to 104 F.; the resonance of both lungs was diminished, and a diagnosis of pneumonia in the midchest was made. On April 14 the red blood cells numbered 3,640,000; this count gradually returned to normal. On April 16 his temperature became normal, but he was noisy and said that smoke was rising from the bed. After this date there was rather rapid improvement; by April 22 his condition was entirely clear, and he was only somewhat tense and anxious. On May 2 he was released from the hospital as recovered.

The bromide levels of the blood serum were 400, 241, 133 and 68 mg. per hundred cubic centimeters on April 13, 16, 20 and 27 respectively.

Because of the high bromide level of the blood serum, the factor of intoxication is most outstanding. However, the dehydration and the pneumonia may well be considered as contributing factors.

CASE 13.—B. D., a woman aged 46, was admitted to this hospital on March 8, 1938. One of her 2 brothers died in a mental disease hospital. The patient had been working very hard in supporting an invalid husband and an alcoholic brother, besides herself. About eight weeks prior to admission she began to complain of weakness and numbness of her right side. On medical advice she went to bed and received for sedation 2 teaspoonfuls of elixir of three bromides before each meal and 6 grains (0.39 Gm.) of phenobarbital daily. This medication was soon changed to 1 teaspoonful of the bromide three times a day and $8\frac{1}{2}$ grains (0.55 Gm.) of phenobarbital daily. Two weeks prior to admission she began to eat sparingly, and during the five days preceding admission she took practically no nourishment. She became stuporous, deluded and hallucinated and was brought to this hospital.

On admission she was incontinent, confused and fearful of dying. She had the sensation of floating on thin air and expressed the belief that her spirit was separated from her body.

Her temperature was 100 to 103 F. There were dulness and diminished breath sounds over the base of the right lung, and the roentgenographic signs were suggestive of bronchopneumonia. She also had cystitis, with burning and frequency and with pus and red blood cells in the urine.

The bromide levels of the blood serum on March 9, 14, 21 and 30 were 197, 118, 60 and 0 mg., respectively, per hundred cubic centimeters.

The patient's condition improved gradually, and thirty-two days after admission she was released from the hospital as completely recovered from the psychosis.

Insufficient nourishment and pulmonary and bladder infection were in this case debilitating factors of probable significance. Constitutional weakness, overwork and financial worries are also to be taken into account. It is to be considered, furthermore, that besides bromides the patient also took considerable amounts of phenobarbital.

INVOLUTIONAL CHANGES AS A PREDISPOSING FACTOR

In the following case psychiatric changes in connection with the menopause seem to have complicated the picture of bromide intoxication.

CASE 14.—C. J., a woman aged 43, was transferred to this hospital from a general hospital on July 6, 1937. One brother has been in a mental disease hospital for twenty years. About three years previous to admission the patient began to suffer from periods of depression, which gradually increased in frequency and severity. Early in the year of admission menstruation became scanty, and at the same time she complained of many disturbances, such as dyspnea, vertigo, indigestion and palpitation. In May 1937 she was taken to a general hospital, where she expressed ideas of unworthiness and claimed that the food was poisoned. She also made a suicidal attempt there.

On admission to this hospital she was confused and disoriented. She was unable to complete sentences. Later she became agitated, and she was fearful that she might do something to hurt herself or her children. She refused food and often induced vomiting artificially. She appeared to respond to auditory and visual hallucinations.

The results of physical examination were essentially without significance except for deafness and a somewhat enlarged heart.

The bromide levels of the blood serum were 150, 144, 105, 48, 43, 37, 36, 33 and 24 mg. per hundred cubic centimeters on July 14, 19 and 27 and August 9, 11, 13, 16, 20 and 25 respectively.

The improvement of the patient was gradual. On Nov. 13, 1937 she was, however, sufficiently well to be tried on a visit. On January 15 she reported to the hospital for reexamination. She was having short periods of confusion and bewilderment and was mildly depressed.

Early in April of the following year the patient died of burns, sustained when her dress caught fire while she was burning some refuse in the back yard. While still conscious she stated that this had been accidental.

The diagnosis of involutional melancholia, which preceded the use of bromides in this case and continued after the signs of intoxication disappeared, is obvious. Heredity may have been a predisposing factor. In view of the fact that the patient suffered from depression and previously had made a suicidal attempt, it may be questioned whether her death was purely accidental.

CASE 15.—C. R., a woman aged 40, was admitted to this hospital on July 29, 1938. During the two years preceding her present illness her menstrual periods were irregular, the patient having at times menorrhagia and at other times dysmenorrhea, which required rest in bed and application of heat. During the same period she was restless, irritable and upset and had crying spells. About a year prior to admission she went to the outpatient department of a general hospital with complaints of blurred vision and headaches, accompanied by "peculiar feelings." She received "medicine for her nerves," which she was taking indiscriminately.

On admission she was restless, incontinent, confused and disoriented. She was afraid that the water was poisoned and refused to drink it. She thought that her enemies had blinded her boy. She had a rapid heart rate and hyperactive reflexes, but no other physical signs.

The bromide levels of the blood serum on July 30 and August 11 and 22 were 254, 60 and 33 mg., respectively, per hundred cubic centimeters. She was released from the hospital on Feb. 25, 1939. Clinical examination one year later did not reveal any gross signs of psychosis, but she complained of headaches and blurred vision and had occasional temper tantrums.

The complaints preceding and following the bromide episode were apparently indicative of early involutional changes. The mental condition in this case was much milder than that in case 14.

CASE 16.—C. P., a man aged 48, was admitted to the Boston Psychopathic Hospital on Jan. 27, 1941 and was transferred to this hospital on January 29. There was a history of several years' duration of such complaints as depression, "foglike" states, pain about the heart, choking spells, insomnia and fatigability. Because of these disturbances, the patient's business (shoe repair) gradually decreased, and finally he sold his shop, two years before his present illness. Since that time he had stayed around the house, doing practically nothing. His condition became worse. Finally he became confused and excited. There was a vague history of the patient's having taken "pills" for insomnia for two or three years.

On admission he was somewhat confused; his speech was slurred, but relevant and coherent. He was apprehensive and bewildered. He had paranoid notions that people were trying to harm him and that they were speaking about him in a sexually insulting and profane manner.

Neurologically, he showed dilated pupils, which reacted poorly to light, tremor of the fingers, some swaying on performance of the Romberg test and moderate dysdiadokokinesis. On January 31 the bromide level of the blood serum was 112 mg. per hundred cubic centimeters.

There was rapid clearing of all neurologic signs and signs of psychosis, but the hypochondriacal complaints persisted. He was released on a year's trial visit as improved on March 2, 1941.

The complaints preceding the incidence of bromide intoxication, and in part persisting after the clearing up of this condition, were clearly related to involutional changes.

CASE 17.—L. L., a woman aged 46, was admitted to this hospital on Sept. 11, 1937. Her father was alcoholic and died of tuberculosis. The patient had tuberculosis of the spine at the age of 12 years. When she was 20 she began to "run about with a 'wild bunch of men.'" She also began to take various drugs. In 1919 she made a suicidal attempt and was admitted to this hospital. At that time a diagnosis of psychosis due to morphinism was made. Not much was known about her adjustment in subsequent years except that in 1922 she had an illegitimate pregnancy and she frequently used drugs.

Six months previous to admission she had amenorrhea. On Sept. 7, 1937 she was found in a deep stupor, from which she could not be aroused, and she was taken to a general hospital. Four days later she was brought to this hospital.

On admission she was disoriented and misidentified people. Her memory was grossly impaired. She saw black people and an Indian with feathers in his hair. She expressed the belief that people were trying to kill her.

She appeared poorly nourished and severely dehydrated. There were pronounced kyphosis and scoliosis, deformity of the chest, displacement of the heart to the right and a systolic murmur over the base. The tendon reflexes were hyperactive.

The bromide levels of the blood serum on September 15, 20 and 27 were 195, 151 and 69 mg., respectively, per hundred cubic centimeters.

On Oct. 7, 1937 the patient was found to have recovered from the acute symptoms of psychosis, and she was discharged on a year's trial visit. About two months after leaving the hospital she complained of "hot flashes," nervousness and prolonged uterine hemorrhages.

Before the expiration of the year's trial visit, on July 27, 1938, she was returned to this hospital in a state of fear and with vivid hallucinations. The bromide levels of the blood serum on July 28 and August 2, 8, 13 and 22, were 327, 321, 260, 106 and 36 mg., respectively, per hundred cubic centimeters. She was again released from the hospital on Aug. 30, 1938.

Subsequently, the patient had two more admissions to this hospital: one in 1940, with the diagnosis of "psychosis due to phenobarbital," and one in 1941, when the diagnosis was "no psychosis; addiction to amytal."

There were many factors of probable etiologic significance in the case of this extremely maladjusted woman, so that it is difficult to decide which is to be considered the most important. The two episodes of bromide intoxication were coincident with the menopause. The following factors have also to be taken into account: (1) poor heredity; (2) chronic maladjustment, which may have been largely a reaction to her physical deformity; (3) personality change, at the age of 20; (4) addiction to various drugs (morphine, amytal, phenobarbital), which led to state hospital admissions, in addition to the two bromide episodes, and (5) severe physical debilitation with dehydration at the time of admission.

In this group, in which involutional changes are considered as a dominant contributing factor, belong the cases of 3 women and 1 man. Their ages were between 40 and 48 years, with an average of 44.2 years. The highest readings for the bromides of the blood serum ranged from 112 to 254 mg. per hundred cubic centimeters, with an average of 160 mg. per hundred cubic centimeters. In case 14 there were definite symptoms of involutional melancholia. In cases 15 and 16 increased fatigability and hypochondriac complaints, such as blurred vision and headaches, prevailed. In case 17 the menopausal disturbances were somewhat obscured by a number of other pathologic features (psychopathic personality; drug addiction).

RELATIVELY UNCOMPLICATED BROMIDE INTOXICATION

The remaining 4 cases fall into this group. Although a psychiatrically significant condition was present in each case, the relation of such a condition to the symptoms of bromide intoxication, if any, is less clear

than in the previously reported cases. Brief summaries of these cases are now given.

CASE 18.—M. C., a woman aged 31, was admitted to the Boston Psychopathic Hospital on Sept. 29, 1941 and was transferred to this hospital on October 7. The patient had had epileptic seizures since infancy. She had been treated with phenobarbital and dilantin, to which a few months before admission bromide was added. She took the latter in solution, without measuring the dose. Before her admission to the hospital she was noted to be bumping into furniture. Then she became confused and had auditory and visual hallucinations.

The bromide levels of the blood serum on October 2, 11, 17, 27 and 31 were 310, 199, 116, 60 and 35 mg., respectively, per hundred cubic centimeters. On admission she was fearful and spoke in an incoherent fashion, stating that people were accusing her of sexual misbehavior. Her condition cleared rapidly. On November 8 she was completely recovered from the psychosis and was released from the hospital. While she was out of the hospital she had frequent seizures and was treated again with bromides. The only untoward signs she observed were itching of the palms and soles and acne-like eruptions on her face and neck.

In this case the toxic effect of the bromide was the outstanding factor. The bromide level of the blood serum three days after admission was still 310 mg. per hundred cubic centimeters. It is questionable whether or not epilepsy can be regarded as an important contributing factor. Some authors claim that epileptic persons have a greater than normal tolerance for bromides.² On the other hand, confusion and twilight states are frequent in cases of epilepsy, and it may be difficult to differentiate clearly these symptoms from those of a bromide intoxication.

CASE 19.—A. L., a woman aged 28, was admitted to this hospital on Aug. 28, 1938. Data on the past history were scanty. She was married ten years ago, but for the past five years she had been going out openly with another man. Ten months ago she was separated from her husband. She had 1 living child and had had 1 stillbirth and 1 miscarriage. She had been a heavy user of bromo-seltzer (a preparation containing sodium bromide, acetanilid and caffeine) for the last nine years. Three or four weeks previous to admission she was observed to be acting queerly. Her walk was staggering, and her speech became difficult to understand. She expressed the belief that the neighbors were calling her evil names.

On August 21 she was taken to a general hospital, where there developed the delusion that she was being framed and she became wildly excited.

On admission to this hospital she was ataxic and confused and talked incoherently in a husky voice. She was fearful and expressed the belief that she was going to die. She was disoriented, and her memory was defective.

The bromide levels of the blood serum on August 24, 30 and 31 and on September 6 were 247, 129, 46 and 0 mg., respectively, per hundred cubic centimeters. On admission large amounts of bromide were found in the gastric con-

2. Bing, R.: *Textbook of Nervous Diseases*, St. Louis, C. V. Mosby Company, 1939, pp. 711-713. Novick, R. G.: *Study of the Treatment of Epilepsy*, Illinois M. J. 74:366-369, 1938.

tents. Two weeks after admission to this hospital her condition was completely clear. She was discharged from the hospital on Sept. 25, 1941, as recovered.

There is sufficient indication of neurotic difficulties in this case, but the relation of these disturbances to susceptibility to bromides is questionable.

CASE 20.—E. D., a woman aged 37, was transferred from a general hospital to this hospital on Sept. 20, 1940. Since the beginning of August 1940 the patient had nursed her sick husband, staying up nights. In addition, she had to take care of the household and the children. She began to take Stanback tablets, each tablet containing 7 grains (0.46 Gm.) of potassium bromide. About September 10, according to one report, she took 50 tablets (22.7 Gm.) within three days and, according to another, 300 tablets (136.5 Gm.) within one week. She became drowsy, and on September 12 she was taken to a general hospital, where she became confused and hallucinated.

On admission to this hospital the patient appeared ill and exhausted. Speech was retarded and slurred, and the gait was unsteady. She was somewhat disoriented, but there was no evidence of hallucinations. Her face and neck were covered with an acne-like eruption. The deep tendon reflexes were hyperactive, and there was a positive Romberg sign.

The bromide levels of the blood on September 21 and 26 and October 18 were 199, 98 and 64 mg., respectively, per hundred cubic centimeters.

One week after admission all physical and mental symptoms had subsided. She was discharged from the hospital as recovered on October 23.

This case appears to be one of uncomplicated bromide intoxication.

CASE 21.—E. B., a woman aged 45, was brought to this hospital from a general hospital on April 14, 1939. The patient had always been an unstable person, subject to severe emotional upsets. At the beginning of March 1939 she was restless, suffered from headaches and received some bromides. On March 10 her headaches were diagnosed as due to sinus trouble, and she was admitted to a general hospital. There she received three bromides (dose not stated). During the last week there the tentative diagnosis of "psychosis on an organic basis, with diffuse cerebrospinal lesions" was made, and she was referred to this hospital.

On admission she appeared drowsy and spoke in a monotonous voice, with some tendency to incoherence and irrelevance. Her mood was that of depression. She stated that people were accusing her of having an illegitimate child. She was hallucinated and saw biblical scenes. She was only partially oriented, and her memory was defective.

Neurologically, she had spells of strabism and ptosis of the eyelids, which disappeared. The tendon reflexes were somewhat diminished.

The bromide levels of the blood serum on April 17, 20, 21, 22 and 25 and on May 1 and 8 were 269, 207, 171, 56, 54, 22 and 0 mg., respectively, per hundred cubic centimeters.

There was gradual improvement in the patient's condition. On May 16, 1939 she was approved for one year's trial visit. By that time she was completely clear.

No definite relationship appeared to exist between the complaints preceding bromide intoxication and the psychotic episode.

Of the 4 patients in this group, 3 were women and 1 was a man. They belonged to a younger age group than did the other patients of this study, their ages ranging from 28 to 45 years, with an average of 35.2 years. These 4 patients presented no major gross contributing factors comparable to those reported for the other groups. There was indirect evidence that in this group the bromide factor may have been more important than in the other groups. The averages of the highest bromide levels in the blood serum for the major groups with complicating factors were as follows: arteriosclerosis, 180 mg.; alcoholism, 170 mg., and involutional changes, 160 mg. per hundred cubic centimeters, while for the present group this value was considerably higher, namely, 281 mg. per hundred cubic centimeters.

COMMENT

The main purpose of this study is to shed light on the significance of predisposing factors in cases of bromide intoxication with psychotic symptoms. Before the main topic is discussed, a number of other observations gathered from my case material may be mentioned.

The patients in this series belonged to an age group ranging from 28 to 75 years, with an average of 49.5 years. This incidence is largely in agreement with the figures given by Moore, Sohler and Alexander,³ who stated that "the greatest incidence of bromide intoxication occurs between 40 and 60 years of age."

Of the 21 patients, 15 were women, and only 6 were men. Although the group is too small to allow one to draw any statistically valid conclusion, the marked prevalence of women in the group is suggestive. A similar distribution of the sexes for bromide intoxication has been reported in the literature by several authors. Moore, Sohler and Alexander,³ in reviewing 100 cases of bromide intoxication previously reported in the literature, found 64 women and only 36 men. In each of my larger subgroups the number of women dominated, with the exception of the cases in which alcoholism was a complication.

The history related to the use of bromides, i. e., the dose and the duration of use of the drug, was in most instances rather vague in my material. The highest readings of bromide levels in the blood serum obtained for the patients ranged from 60 to 400 mg. per hundred cubic centimeters, with an average of 201 mg. per hundred cubic centimeters. It is, however, to be noted, that these figures do not actually represent the highest level ever reached by the patients. Often there was several days' delay in the bromide determination. In addition, several of the patients were transferred from general hospitals, and thus the bromide

3. Moore, M.; Sohler, T., and Alexander, L.: Bromide Intoxication: Review, *Confinia neurol.* 3:1-52, 1940.

level was already below the maximum when they arrived at this hospital, except for those patients who received additional bromide medication in the general hospital. This consideration appears significant in evaluating the various statements occurring in the literature with regard to the toxic level of bromides in the blood serum. The disagreement which exists on this point may be due, in part, to differences in the length of time elapsing between the discontinuance of bromide intake and the laboratory determination of the bromide level of the blood serum. It is, however, safe to assume that the actual toxic level is considerably higher than is generally reported in the literature. In most instances it is impossible to obtain the true peak of the bromide level reached in a given case. It would be possible, however, to arrive at an approximate estimate of the true peak by making a correction based on the average rate of elimination and the time elapsing between the cessation of bromide intake and the laboratory test. Granted that the estimated figures are inaccurate, such figures would still be more representative and afford a better basis for comparison than the data available in the literature at present.

The psychotic symptoms in my cases were fairly uniform and consisted mainly of three types:

1. Clouding of consciousness (confusion, disorientation and drowsiness) was the most constant symptom.

2. Hallucinatory and delusional experiences were present in the majority of cases. The hallucinations were visual and auditory, the former being somewhat more frequent and more vivid. The delusions were never systematized to any extent, and their content almost invariably referred to a threat to the patient's life. ("People are trying to kill me"; "they are trying to poison me," etc.)

3. The emotional reaction was typically that of fear, and occasionally that of excitement.

Of the neurologic signs, thickened speech and ataxic phenomena were the most frequent. There were no typical and consistent changes in the reflexes in these cases. The tendon reflexes were occasionally increased, but at other times they were diminished or unchanged.

Acneform skin eruptions ("bromide rash") were observed in only a few cases, and, judging from this material, the symptom is far from being as characteristic and frequent as some writers have claimed. On the other hand, it is possible that such a common lesion is not recorded by the physician unless it is of considerable extent.

The psychiatric picture as described is clearly that of an organic psychosis. The differentiation of the symptomatology from that of toxic, infectious, metabolic and other organic conditions which are characterized by clouding of consciousness and delirium is hardly possible on the basis of the clinical picture alone. The psychiatrist usually feels

confident in making a diagnosis of "psychosis due to bromides" only if the laboratory tests reveal a sufficiently high bromide level in the blood. Even in the latter case, however, often some reservation is made as to the final diagnosis pending the results of the therapeutic test. This is, indeed, reasonable, since the acute symptoms easily can mask an underlying condition of even greater etiologic significance than the intoxication itself.

In connection with the problem of differential diagnosis, it seemed to me worth while to inquire what are the common indications which lead the psychiatrist to suspect bromide intoxication in a given case. During the five year period to which the present study refers, the physicians requested bromide determinations in the cases of 83 newly admitted patients, in addition to the 21 cases which are discussed in this paper. An analysis of these cases reveals that bromide determinations were occasionally requested because it was known that the patient had been taking the drug for some time. In most instances, however, the request was made because a patient showed clouding of consciousness and delirium. The final diagnosis in 31 of the 83 cases was cerebral arteriosclerosis. The patients showed much confusion, disorientation and bewilderment. The other cases belonged to the following diagnostic categories: psychosis due to drugs (other than bromides, chiefly barbitol), alcoholic hallucinosis, psychosis due to metabolic disease (toxic delirium, puerperal psychosis, etc.), psychosis with syphilitic meningo-encephalitis, dementia paralytica, involutional melancholia, psychoneurosis (chiefly hysteria with confusion), schizophrenia (acute catatonic states with clouding of consciousness) and manic-depressive psychosis.

In a survey of the cases in which bromide intoxication was suspected, two points stand out clearly: 1. In the great majority of cases the same conditions were present which appeared to be predisposing and complicating factors in the series of the 21 cases in which the diagnosis of psychosis due to bromides was actually made. In other words, the organic reaction types (arteriosclerotic, alcoholic, infectious, toxic, etc.) make up a large percentage of the conditions in cases in which bromide intoxication is suspected, as well as in cases of actual bromide intoxication. The significance of this relationship will be clarified later. 2. In the cases in which bromide intoxication was suspected, there were, in addition to organic psychosis, a considerable number of functional mental disorders, particularly schizophrenia (13 cases), while in my group of 21 cases of actual bromide intoxication there was none in which schizophrenic psychosis complicated the clinical picture. The reason for this is obvious. In cases of schizophrenia, particularly the catatonic type, an initial confusional picture which somewhat resembles organic delirium is not infrequent. During the observation period (ten to forty days), that is,

before the official diagnosis is made, the underlying schizophrenic symptomatology will almost invariably appear, and thus the first diagnostic impression is corrected before the final diagnostic label is assigned to the case.

In regard to the factors predisposing to bromide intoxication several points stand out in the present material. Among the 21 cases reported there were only 4 in which gross predisposing factors of definite etiologic significance could not be demonstrated. The predisposing factors, only the most outstanding feature in each case being considered, were: advanced arteriosclerosis, 5 cases; severe alcoholism, 4 cases; extensive necrosis of the brain, 1 case; untreated syphilis, 1 case; severe physical debility (acute infection and dehydration), 2 cases, and involutional complications, 4 cases. To several of the aforementioned conditions a certain etiologic significance for bromide intoxication has been ascribed by various authors. Arteriosclerosis was mentioned by Sharpe,⁴ Preu, Romano and Brown,⁵ Burns,⁶ Howe⁷ and Wagner and Bunbury⁸; alcoholism, by Burns,⁶ Sharpe,⁴ Hunt,⁹ Wainwright¹⁰ and Diethelm¹¹; syphilis, by Wainwright,¹⁰ Sharpe,⁴ Burns⁶ and Diethelm¹¹; organic disease of the brain, by Levin,¹² and infections, by Preu, Romano and Brown.⁵

It is usually assumed that some of the aforementioned conditions are predisposing factors in bromide intoxication because of defective renal function, which hinders the elimination of bromides. Although this explanation may be applicable in certain cases, it is not probable that major importance generally can be ascribed to this factor. If the decrease of bromide elimination is the main factor, one would expect high bromide levels in the blood in these cases. This, however, cannot

4. Sharpe, J. C.: Bromide Intoxication, *J. A. M. A.* **102**:1462-1465 (May 5) 1934.

5. Preu, P. W.; Romano, J., and Brown, W. T.: Systematic Psychoses with Bromide Intoxication: Their Occurrence in Southern New England, *New England J. Med.* **214**:56-62, 1936.

6. Burns, G. C., and Henderson, J. L.: Bromide Intoxication, *California & West. Med.* **46**:392-395, 1937.

7. Howe, H. S.: Tonics and Sedatives in Neurologic Practice, *New York State J. Med.* **39**:31-41, 1939.

8. Wagner, C. P., and Bunbury, D. E.: Incidence of Bromide Intoxication Among Psychotic Patients, *J. A. M. A.* **95**:1725-1728 (Dec. 6) 1930.

9. Hunt, E. L.: Deleterious Effects of Bromide Treatment in Diseases of the Nervous System, *M. Rec.* **100**:103, 1921; *New York State J. Med.* **21**:255, 1921.

10. Wainwright, C. W.: Bromide Intoxication, *Internat. Clin.* **1**:78-95, 1933.

11. Diethelm, O.: On Bromide Intoxication, *J. Nerv. & Ment. Dis.* **71**:151-165 and 278-292, 1930.

12. Levin, M.: Bromide Delirium and Other Bromide Psychoses, *Am. J. Psychiat.* **12**:1125-1162, 1933.

be substantiated on the basis of my material, since in many cases psychotic symptoms occurred with moderate elevation of the bromide level of the blood serum.

My data suggest another mechanism for the etiologic significance of the aforementioned predisposing conditions. It is remarkable that my cases, with the exception of the group with involutional changes, were complicated by organic conditions which in themselves may lead to organic psychoses with symptoms closely resembling those of bromide intoxication. Several of my patients manifested signs of beginning organic psychosis. Others showed decidedly at least the organic symptoms of such conditions as are known to be conducive to organic psychosis. My hypothesis, then, is that there is a synergistic relationship between the underlying organic pathology and the phenomena referable to bromide intoxication, both leading toward psychotic manifestations of the same type. They reenforce each other and lead finally to a picture of delirium. In this connection, it is interesting to remember that the 3 male alcoholic patients in the present series all had previously had several incidents of delirium tremens. There may be justification for the assumption of Diethelm¹¹ that "certain constitutional make-ups seem to react easily with delirium to toxic and organic damages."

The foregoing generalization applies to a certain extent, also, to the cases with involutional complications. The symptoms of involutional psychosis are often confusion, bewilderment, fear and paranoid notions and thus are not dissimilar to those seen in bromide intoxication.

If the present investigation had revealed only that some psychiatric condition is almost invariably present in cases of bromide intoxication, my results would have been inconclusive. It would have shown only the obvious, namely, that bromides are taken largely by persons suffering from some nervous or mental disorder. The preexisting conditions in our cases, however, were not neuropsychiatric disturbances of any type, but conditions which are known to produce by themselves symptoms closely resembling those of bromide intoxication. This gives the clue to the interpretation previously offered.

The most striking result of the present study is that gross morbid conditions were present in the great majority of the cases and that these disturbances were in all instances severe and meaningfully related to the psychotic symptoms. This result is the more significant since all such cases in which the official diagnostic label indicated some other factor complicating bromide intoxication were excluded from this study. That the bromide intoxication played a role in bringing about the psychotic episode is clear from the fact that the patients recovered from the psychosis or improved considerably after they were free of bromides. My data, however, seem to suggest that a distinct etiologic significance is to be ascribed to the preexisting pathologic condition.

SUMMARY

Twenty-one consecutive patients admitted to the Worcester State Hospital during a five year period with a condition diagnosed as psychosis due to bromides were studied from the point of view of underlying gross predisposing factors.

The patients belonged to an age group ranging from 28 to 75 years, with an average of 49.5 years. There was a distinct prevalence of women in the group (15 women; 6 men).

The average level of bromides in the blood serum was 201 mg. per hundred cubic centimeters, with a range of 60 to 400 mg. per hundred cubic centimeters. Attention is called to the fact that this level, as well as the toxic levels given by the various authors in the literature, are in general considerably below the actual peak. The time elapsing between the cessation of bromide intake and the rate of elimination has to be considered in order to estimate the true height of the bromide level in the blood serum.

Of the mental symptoms, clouding of consciousness was found to be the most constant. Hallucinations and delusions were present in the majority of the patients. The delusional ideas referred almost invariably to some threat to the patient's life. The emotional reaction was that of fear, and occasionally that of excitement. There were no typical neurologic changes except thickened speech and ataxic phenomena. Pronounced "bromide rash" was considerably less frequent than most authors have reported.

In 17 of the 21 patients severe and etiologically significant predisposing factors were present. These were: advanced arteriosclerosis, 5 patients; severe alcoholism, 4 patients; untreated syphilis, 1 patient; necrosis of the brain, 1 patient; physical debility (infection, dehydration), 2 patients, and involutional complications, 4 patients. The organic lesions in all patients were in a rather advanced stage. Several of these patients showed signs of a beginning organic psychosis previous to the use of bromides.

The hypothesis is advanced that there is a synergistic relationship between the phenomena referable to bromide intoxication and the underlying organic lesions.

It is concluded that in the great majority of the cases a distinct etiologic significance is to be ascribed to the preexisting pathologic conditions.

Worcester State Hospital.

MENINGEAL GLIOMATOSIS SECONDARY TO INTRAMEDULLARY GLIOMA

ROMA AMYOT, M.D.

MONTREAL, CANADA

Since Ollivier's¹ publication in 1837, primary sarcomatosis of the meninges, a diffuse infiltration of the cerebral and spinal leptomeninges by a tissue chiefly cellular and of sarcomatous appearance, has been known. Many observations confirming the existence of such a process were published. Then every diffuse neoplastic process in the leptomeninges, apparently primary, was believed to be "sarcomatosis of the meninges."

Leusden,² in 1898, reported a case of a similar lesion of the leptomeninges, microscopic examination of which showed round cells which looked like "sarcomatous cells" but were associated with bundles of fibers. Not daring to deny the idea of primary sarcomatosis, Leusden, nevertheless, suggested a possible gliomatous participation, and even origin, and designated the diffuse meningeal tumor in his case by the name of gliosarcoma.

Gradually, however, the importance of the concept of "sarcomatosis" diminished. The invasive potentialities of the intracranial glioma were increasingly taken into account. It was even concluded that the meningeal dissemination of a neoplastic process is usually secondary to the presence of a glioma and that primary sarcomatosis of the leptomeninges is rare. Therefore the idea of secondary meningeal gliomatosis superseded that of so-called primary meningeal sarcomatosis. Verdun³ contributed greatly to the concept of gliomatosis of the meninges and expressed the assumption that the process of gliomatosis spreads in the leptomeninges by way of the cerebrospinal fluid after rupture of the ependymal surface.

It must be emphasized that the precise identification of the diffuse growth in the meninges was greatly facilitated by the more complete knowledge of the microscopic appearance of gliomas.

From the Hôpital Notre-Dame.

1. Ollivier, C. P.: *Traité des maladies de la moelle épinière*, ed. 3, Paris, Méquignon-Marvis & fils, 1837, vol. 2, p. 490.

2. Leusden, P.: Unusual Case of Glioma of the Spinal Cord, *Beitr. z. path. Anat. u. z. allg. Path.* 23:69, 1898.

3. Verdun, M.: *Etude anatomo-clinique sur les complications méningées cérébrales*, Thesis, Paris, no. 201, 1912.

By their personal investigations and the histologic survey of cases previously recorded, Bailey and Cushing⁴ proved that the majority of diffuse gliomas of the meninges are medulloblastomas originating in the cerebellum. Thus, according to these authors, the first case reported, that of Ollivier, was an instance of meningeal invasion from a cerebellar medulloblastoma. But this rule is not without exception, as was illustrated in subsequent papers, particularly the interesting publication of Cairns and Russell.⁵ These authors reported 8 cases of intracranial and intraspinal gliomatosis of the meninges, which included 3 cases of medulloblastoma and 5 cases of other gliomas: 1 astrocytoma of the thalamus, 1 of cerebellar ependymoma, 1 of cerebral glioblastoma, 1 of unclassified glioma and 1 of neuroepithelioma of the retina. Cairns and Russell also cited a case of oligodendroglioma reported by Cushing, and a case described by Van Wagenen and another by Töppich in which the meningeal invasion came from a papilloma. Therefore it must be concluded that the intracranial glioma, whatever its histologic appearance, and not medulloblastoma alone, can invade the ventricles and the subarachnoid spaces and infiltrate the meninges.

In an excellent paper, Kernohan, Woltman and Adson⁶ stated:

The structure of the spinal cord is essentially the same as that of the brain; therefore, one would expect at least some similarity among the neoplasms arising from them.

If this is so, one can presume that the intramedullary glioma, sharing the same characters as the encephalic glioma, is able to invade the meninges and give rise to the anatomicoclinical picture of "meningeal sarcomatosis." In fact, the phenomenon has been observed. But the cases reported are few.

We could collect only 9 such cases from the literature. Intramedullary glioma is not frequent: Indeed, intramedullary tumors, which are not gliomas alone, represent about 22 per cent of intraspinal tumors according to Elsberg,⁷ who reported statistics based on 100 cases of his own and collected cases of other authors. In a recent article

4. Bailey, P., and Cushing, H.: Medulloblastoma Cerebelli: A Common Type of Midcerebellar Glioma of Childhood, *Arch. Neurol. & Psychiat.* **14**:192 (Aug.) 1925; Classification of the Tumors of the Glioma Group on a Histogenic Base with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926.

5. Cairns, H., and Russell, D. S.: Intracranial and Spinal Metastasis in Gliomas of the Brain, *Brain* **54**:377 (Dec.) 1931.

6. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intra-Medullary Tumors of the Spinal Cord: A Review of Fifty-One Cases with an Attempt at Histologic Classification, *Arch. Neurol. & Psychiat.* **25**:679 (April) 1931.

7. Elsberg, C.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, Inc., 1925.

Rasmussen, Kernohan and Adson,⁸ who observed 557 cases of intra-spinal tumor, reported 67 cases of intramedullary neoplasm, mostly glioma, an incidence of 11.5 per cent. On the other hand, one can assert that meningeal gliomatosis, or the diffuse or nodular meningo-ventricular metastasis arising from an intramedullary glioma, is a rare, almost an exceptional, phenomenon. Kernohan⁹ observed such a process only once in 52 intramedullary tumors which he studied.

One must not be amazed if the medical literature is not crowded with similar cases. The two first cases were reported, we believe, by Roux and Paviot¹⁰ and by Fränkel¹¹ in 1898. The patient of Roux and Paviot, aged 45, had a glioma in the cervicothoracic segment of the cord; the meningeal infiltration extended as far as the cauda equina. There were nodules on the roots, which were surrounded by neoplastic tissue. The authors did not mention the condition of the intracranial meninges.

The patient of Fränkel, aged 33, had a glioma of the cervical portion of the cord. The spinal meninges were invaded down to the cauda equina; neoplastic nodules were observed on the roots; the medulla was also surrounded by neoplastic tissue and the pia mater of the base of the brain was thickened; anisocoria had been observed during the last period of the illness, which ended two months after the onset.

The patient of Fischer,¹² aged 8 years, had an intramedullary tumor in the lumbar region; some metastatic growths were observed in the third ventricle and in the head of the caudate nucleus; the medulla, the floor of the fourth ventricle and the corpora quadrigemina were also infiltrated. The patient died eight months after the onset. Clinical examination had shown inequality of pupils and bilateral papilledema.

Schlagenhauser¹³ reported the case of a woman aged 37 who had a large tumor in the cervical segment of the cord; the cerebral and spinal meninges had been infiltrated by the tumor; the ependyma was

8. Rasmussen, T. B.; Kernohan, J. W., and Adson, A. W.: Pathologic Classification with Surgical Consideration of Intra-Spinal Tumors, *Ann. Surg.* **111**:513 (April) 1940.

9. Kernohan, J. W.: Primary Tumor of the Spinal Cord, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, p. 1014.

10. Roux and Paviot: A Case of Tumor of the Spinal Cord: Diagnosis of Position by Means of Radicular Localization, *Arch. de neurol.* **5**:433, 1898; cited by Firor and Ford.¹⁸

11. Fränkel, A.: Tumors of the Spinal Meninges, *Deutsche med. Wchnschr.* **24**:442, 1898.

12. Fischer, O.: *Arch. f. Heilk.* **22**:344, 1901.

13. Schlagenhauser, F.: Intradural Endothelioma in the Upper Cervical Segment, *Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. a. d. Wien. Univ.*, 1902, no. 8, p. 88.

thickened; there was hydrocephalus, and the cranial nerves were embedded in neoplastic masses; optic nerve atrophy, convulsions and coma marked the last phase of the illness.

In the case reported by Grund,¹⁴ that of a boy 11 years old, the condition was diagnosed as tumor of the brain; a cervical intramedullary glioma had infiltrated the cerebral and the spinal meninges; at autopsy a diagnosis of tuberculous cerebrospinal meningitis was made, but after thorough microscopic examination the correct pathologic diagnosis was arrived at. The clinical diagnosis of tumor of the brain was plausible in view of the presence of vomiting, frontal headache, asymmetric pupils, papilledema, nystagmus, bradycardia and increased intracranial pressure. Indeed, an intracranial tumor did exist, but the mistake was with regard to the primary location of the tumor, which was the cord and not the brain.

It must be emphasized here that it was only about 1916 that the potential tendency of gliomas of the central nervous system to extend was suspected. Besides, those tumors of the nerve parenchyma which infiltrate the meninges were persistently designated by the hybrid denomination of "gliosarcoma," used first by Leusden.² The gliomatous nature and origin of the infiltrating tumors of the meninges were not yet accepted.

Rutimeyer¹⁵ reported the case of a man aged 30 who had noticed gradually increasing weakness of both feet with amyotrophy of the legs. Three months after his admission to the hospital, vomiting and headache appeared; there was increased pressure of the spinal fluid, detected by lumbar and ventricular punctures; the fluid coagulated and contained 179 cells per cubic millimeter; autopsy revealed an intramedullary tumor in the sacral portion of the cord and neoplastic infiltration of the spinal meninges. The anatomic condition of the cerebral meninges was not mentioned in the observation. Rutimeyer identified correctly the origin of the gliomatosis, having verified that the neoplastic process of the cord had invaded the subarachnoid spaces after having pierced the pia mater; he recognized also the gliomatous nature of the tumor; however, he expressed the belief that the glioma was malignant, a "glioma sarcomatodes." The denomination is surely not a bad one. Besides, it illustrates how the notion of the nature and origin of the neoplastic dissemination in the meninges evolved in the mind of investigators: It was first thought that the diffuse growth was sarcomatosis; Rutimeyer, in 1920, declared that his case was one of gliomatosis. It came to be

14. Grund, G.: The Diffuse Extension of Malignant Tumors, Especially Gliosarcoma, in the Leptomeninges, *Deutsche Ztschr. f. Nervenhe.* **31**:283, 1906.

15. Rutimeyer, W.: Glioma Sarcomatosis of Spinal Cord with Diffuse Gliomatosis of Spinal Leptomeninges, *Schweiz. med. Wchnschr.* **50**:1201 (Dec. 30) 1920.

believed, then, that gliomatosis was possible; it is known now that the neoplastic infiltration of the meninges is almost always gliomatosis, and not a sarcomatous process.

Kernohan,⁹ of 52 cases of intramedullary tumors, observed infiltration of the tumor in the leptomeninges in only 1, and then over a short distance upward and downward. The tumor was a medullary oligodendroglioma.

Eden¹⁶ cited a case of Forster,¹⁷ that of a medulloblastoma in the lumbar region, which spread through the spinal and even the intracranial meninges.

Eden published the case of a youth aged 19 who had gradually progressive paraplegia with decreased sensation; the paraplegia was flaccid and later spastic, with complete block of the subarachnoid spaces and yellow fluid. Three or four months after onset of the illness, the patient felt numbness of the upper limbs and vomited; there developed some dysarthria, right hemiparesis with headache and diplopia due to weakness of the left external rectus muscle. These troubles vanished. Laminectomy revealed an intramedullary tumor in the lumbar portion and in the conus. The tumor was not removed. Later vision decreased; papilledema was observed, and the patient became deaf and confused; he had convulsions and died about the seventh month of his illness. Autopsy showed a gliomatous "exudate," or growth in the pia-arachnoid over the cerebral hemispheres, which was particularly dense over the base of the brain and around the spinal cord. This gliomatous tissue surrounded the nerve roots. In the lumbar portion of the cord the tumor replaced entirely the medullary tissue and was continuous with the meningeal gelatinous growth. Microscopic examination revealed that the gelatinous material was tumor tissue infiltrating the leptomeninges and invading the sulci of the cerebral cortex, and even the Virchow-Robin spaces. It was obvious that the infiltrating process had its origin in the intramedullary tumor.

The multicellular character of this tumor makes it difficult to place it in any of the usually accepted classifications of gliomas. Its cellular character suggests its inclusion amongst the glioblastoma multiforme group, but the lack of degenerative and characteristic changes in blood vessels seems rather to weigh against this.

We present a case as a typical example of meningeal gliomatosis originating from an intramedullary glioma, with regard both to the clinical picture and evolution and to the anatomicopathologic character. We believe that the clinical and pathologic facts reported may contribute to the study of meningeal gliomatosis arising from intramedullary glioma.

16. Eden, K. C.: Dissemination of a Glioma of the Spinal Cord in the Leptomeninges, *Brain* 61:298, 1938.

17. Forster, E.: Significance of Cell Picture for Diagnosis of Tumors of Central Nervous System and Tumors Originating in Meninges, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 126:683, 1930.

REPORT OF A CASE

Georges G., aged 20, was admitted to Hôpital Notre-Dame on April 10, 1937 for a persistent pain over the sacral region. A suppurative lesion of the right foot, which had been present six years and was probably tuberculous, was treated by immobilization in a plaster cast; except for this condition, the patient had enjoyed good health in the past.

The present illness, until the patient's admission to the hospital, had produced sensory troubles, mostly pain. The pain was now permanent.

In November 1936 the patient had an accident, his buttock having been wedged by a truck. For the following three days pain was felt over the sacral region. Afterward, the pain was present every morning for a few minutes when the patient got up. In January 1937 decrease of sensation was noticed over the left lower limb, which lasted for about fifteen days, followed by numbness over the same region until the time of hospitalization. In February 1937 the pain over the sacrum returned; it later decreased but never disappeared. It was still there, occasionally being very severe, almost unbearable, and irradiating toward the ilium. It was a traction and twitching sensation, which was increased by coughing, laughing, bending the trunk and defecation. It prevented the patient from walking. The left lower limb felt heavier than the right. There was no disturbance of micturition until after a lumbar puncture and injection of iodized poppyseed oil in the subarachnoid space, when vesical retention occurred.

Neurologic Examination.—The spinal muscles on the right side were in permanent contraction. There was no scoliosis and no deformity of the spine, which was otherwise stiff. No neurologic signs were noted over the head and upper limbs. The abdominal reflexes were present, those on the right being stronger perhaps than those on the left. No cremasteric reflex was elicited. Percussion over the sacrum and the fifth lumbar vertebra was painful.

Lower Limbs.—Motor power was normal. Pressure on the left crural nerve at the level of the groin was painful. The Lasègue and Bonnet signs were not elicited.

The anterior muscle group of the left thigh was slightly atrophic. The left patellar reflex was abolished; the right was exaggerated. The left ankle reflex was weaker than the right, which was normal. The right plantar reflex was normal; the left was absent. Sensation to touch was normal. Sensations to temperature and pain were abolished over the inner half of the left leg and the left foot. Sensation to position was normal. Sensation to vibration was decreased over the left leg and the left foot.

Lumbar Puncture.—The first puncture showed a pressure of 200 mm. (with the patient lying down), which rose to 220 mm. on jugular compression and to 350 mm. on abdominal compression and fell to 130 mm. after 10 cc. of fluid had flowed out. The fluid was normal except for a doubtful reaction to the Pandy test. A second puncture, done a month later, showed a pressure of 80 mm., which remained the same on jugular compression but rose to 180 mm. on abdominal compression and fell to zero after 3 cc. of fluid had flowed out. The protein content was 0.04 mg. per hundred cubic centimeters, and the cell count was 11 per cubic millimeter (the second puncture was done about fifteen days after the injection of the poppyseed oil).

Subarachnoid Injection of Iodized Poppyseed Oil.—On injection of iodized poppyseed oil into the spinal canal between the twelfth thoracic and the first lumbar vertebra, the oil flowed down freely to the sacral region. When the patient was placed head down on the x-ray table, one could see the oil moving down to the

twelfth thoracic level, where it stopped and took a trident-like form. One-half cubic centimeter of iodized poppyseed oil, injected in the subarachnoid space between the seventh cervical and the first thoracic segment, remained at this level and was still there three months later.

Operation.—Laminectomy was performed by Dr. William Cone, of the Montreal Neurological Institute. A medullary tumor was observed at the level of the eleventh and twelfth thoracic segments; it had a gliomatous appearance, was infiltrating and diffuse and invaded the subarachnoid space in situ. Dr. Cone carefully removed part of the tumor by suction and curettage.

Evolution.—Immediate improvement followed the operation; the vesical retention and the subarachnoid block disappeared. Roentgenologic treatment was given over the spine from the ninth to the twelfth thoracic vertebra, the total dose being 3,000 r.

Examination twenty days after operation revealed no pain and normal micturition. Genital erections, which had been absent for the last two months, had returned. The patient could turn himself in his bed and bend his head without pain. The neurologic signs, however, remained the same. He left the hospital but was readmitted three months later. He died ten months after the operation and seventeen months after the onset of the illness.

During the second hospitalization both lower limbs became completely paralyzed, and an area of total anesthesia extended to the ninth thoracic segment. One could observe progressive amyotrophy of the limbs. The pain came back; it was occasionally violent and felt over the sacrum, radiating toward both ilia and both lateral aspects of the abdomen.

Later, an intracranial pressure syndrome, consisting of headache, bilateral papilledema, slow pulse, transitory palsy of both sixth cranial nerves and mental confusion with onirism, was observed. The pressure of the fluid was 250 and 400 mm. on two occasions.

Clinical Summary.—Rapidly progressive and extensive paraplegia in a patient aged 20, having its onset with sacral pain, was due to an intramedullary tumor of the lumbar segment, which infiltrated the subarachnoid space in situ and could be observed after laminectomy. The growth was partially removed. Subarachnoid block was present, with the lower level at the twelfth thoracic segment. During the last months of the illness an intracranial pressure syndrome developed.

Macroscopic Appearance of the Tumor.—The lower extremity of the specimen was formed by the cauda equina, of which the nerves, free for a distance of 3 cm., were, at an upper level, surrounded by a growth molded on the anterior aspect of the spinal canal. This growth had a length of 7 cm. and was located in the sacrolumbar region. It budded backward as far as inside the scar of the surgical incision. The tumor was oval in cross section. The anteroposterior axis was 4 to 6 cm. and the transverse axis 3 cm. The anterior aspect alone was covered by the dura mater, which was broken and destroyed over the posterior aspect. As the tumor extended upward it was abruptly reduced in size, its outlines became more regular and its shape cylindric; it was covered at the upper level entirely by the dura mater. Its diameter, which here was 2.5 cm., gradually decreased up to the midthoracic region, where the cord, covered by the dura mater, was of normal volume.

Microscopic Examination.—Examination of sections made at different levels revealed the following lesions: The center of the lumbar growth was necrotic. The anterior half of the tumor was bordered by the dura mater, which was ruptured dorsally, the growth pressing the dura laterally. The cord was entirely

destroyed. One could assume its previous existence by remnants of pia mater and the presence of spinal vessels in the neoplastic mass. The remnants of pia mater were well seen on the left side, where they were fixed to the dura mater by the dentate ligaments; on the right, they were dislocated; dorsally there were none.

The anterior spinal vessels were enlarged, but not deformed; the posterior vessels were displaced. The presence of these vessels embedded in the growth led one to believe that the tumor had destroyed the lumbar segment of the cord from which it arose and that it had extended throughout the meningeal membranes at that level. In a limited area in the middle and anterior portion the growth even penetrated the dura mater completely. The dura mater was ruptured backward, and the growth invaded the operative wound. Near the upper level of the lumbar growth section showed again herniation of the neoplasm backward and through the dura mater, which was normal over the anterior and lateral aspects. The pia mater was well seen except at the back. The structure of the cord was replaced by abnormal tissue, white and dense, similar to that observed in the meninges. In numerous areas the pia mater was pierced by bridges of neoplastic tissue which united the medullary and the meningeal neoplasm.



Fig. 1.—Pathologic specimen.

At the level of the lower segment of the thoracic cord, the tumor was surrounded by the dura mater. The cord was embedded in the growth, and here, again, its former location could be identified by the surrounding pia mater. The thickness of the meningeal growth in the lower portion was twice or three times that in the upper portion.

In the middle and upper thoracic regions, the cord was present and apparently normal. The meningeal infiltration by the tumor surrounded the cord entirely; it decreased gradually upward and could not be seen with the naked eye in the cervical region.

Summary of Pathologic Observations.—A tumor arose in the lumbar portion of the cord, which entirely replaced the parenchymatous tissue in the lumbar and the lower half of the thoracic region. This portion of the tumor was 15 to 16 cm. long. The glioma invaded the leptomeninges all around the cord up to the cervical level and extended downward to surround partially the nerves of the cauda equina. Thus, the meningeal growth formed around the cord a gliomatous sheath, which was 23 to 24 cm. long. In the lumbar region the glioma had ruptured the dura backward for a distance of 8 cm., and thus formed an important growth, which penetrated the surgical wound. The anterior portion of the dura was only locally invaded.

Microscopic Appearance of Neoplasm.—The tumor presented three structural types with all forms of transition: (1) an extremely fibrillar and fasciculate astro-

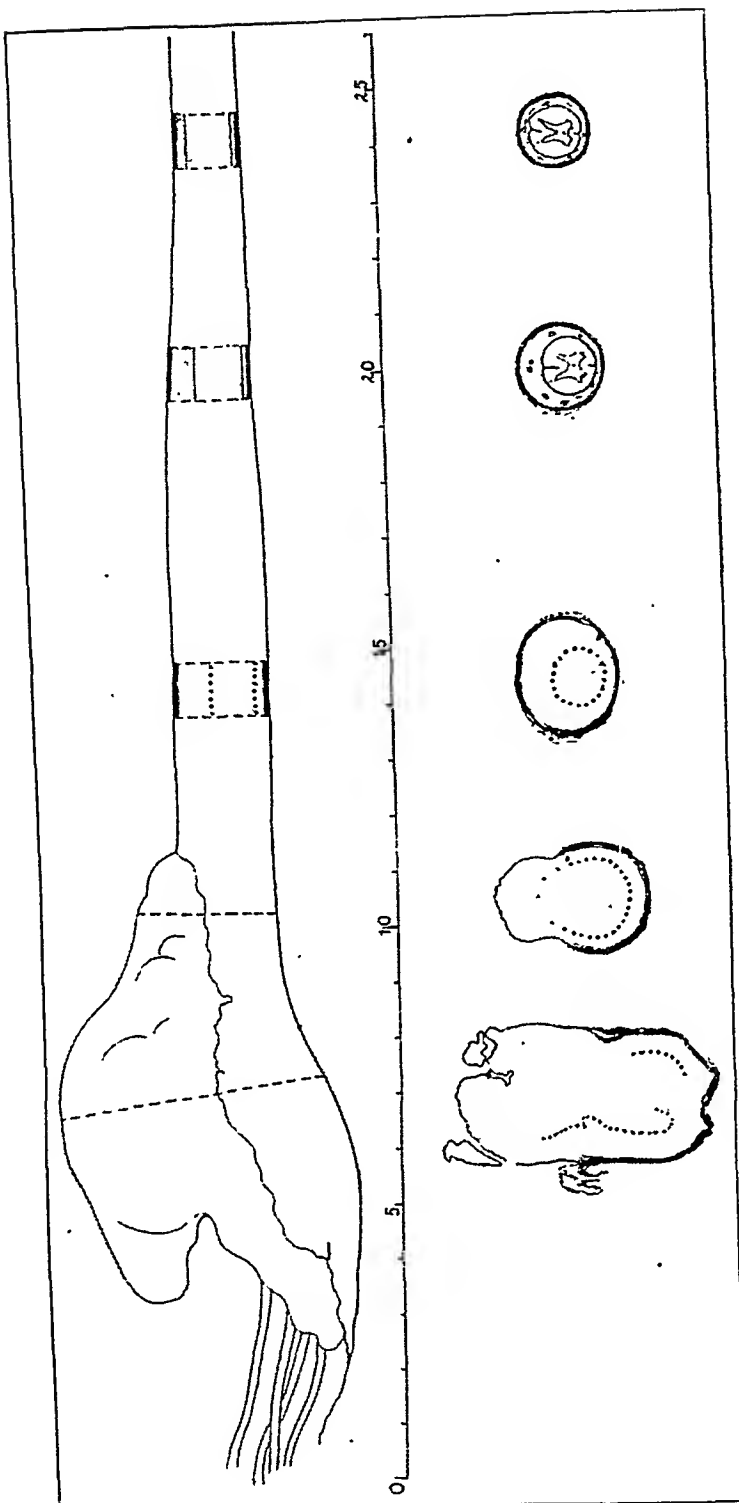


Fig. 2.—Schematic drawing of the medullary tumor. At left: Lateral appearance of the cord. The tumor was located in the lumbar segment of the cord and extended backward through the ruptured dura mater; it partially invaded and surrounded the nerves of the cauda equina. The dura was distended in the thoracic region, but was not ruptured. The distention gradually decreased in the upper thoracic region.

The dotted lines indicate levels at which the transverse sections were taken for histologic examination.

At right: schematic drawing of the transverse sections. The glioma is indicated in gray. In the three lower drawings, the dotted lines show the situation of remnants of the pia. In the two upper drawings the pia mater is normal. The neoplastic tissue fills the subarachnoid space.

cytoma; (2) a fibrillar and reticular astrocytoma, and (3) a neoplasm with round and undifferentiated cells. These three types were diversely distributed at the different levels of the tumor.

Lower Lumbar Portion of Tumor: The large mass in the lumbar enlargement of the cord had a necrotic center, around which the neoplasm was entirely fibrillar and fasciculate (type 1). Some vessels with thick and fibrous walls crossed the neoplastic tissue. The spaces between the vessels were filled with neuroglial fibers, which stained easily and were very dense and were grouped in bundles, passing in every direction. In spots, the fibrils were normally implanted on the vascular walls and radiated around the vessels. The nuclei were scattered in the fibrillar tissue, and the cytoplasm of the astrocytes could hardly be seen. However, some ameboid gliocytes could be observed here and there. The deep region of the neoplasm was surrounded by another, which had a grossly alveolar appear-



Fig. 3.—Lower thoracic region. *P* indicates the pia mater. The lower portion of the photomicrograph shows the infiltrated portion of the cord. The light spots are the granular corpuscles. The upper portion shows the lacunas of the arachnoid filled and distended with extensions of fibrous glioma.

Glial bundles pierce the pia here and there and join the medullary and the meningeal portion of the glioma.

ance (type 2). Here, the neoplastic tissue was crossed and divided by fibrous tracts into more or less thick bundles. The glial fibers were less numerous, and their arrangement was less precise; they gradually lost their parallel formation and appeared as a more or less loose thread. The glial fibrils were less numerous than the nuclei. The nuclei were round and regular, and the stellar cytoplasm was easily stained. This alveolar tissue, poor in glial fibrils and rich in cells, filled the space between the remnants of the pia and the dura, i. e., the whole of the arachnoid. It embedded the anterior roots without invading them; it infiltrated the posterior roots and produced dissociation of their myelinated fibers.

Upper Lumbar Portion and Lower Thoracic Portion of Tumor: Here, the histologic appearance of the tumor was of type 2: reticular in the cord and reticular and alveolar at the periphery, where it invaded the leptomeninges. These two reticular masses were joined together by neuroglial tracts (type 1), which pierced the pia at many spots. In fact, the pia was like a skinmer, through every hole of which passed a glial tract (fig. 3). The areas where the posterior roots emerged were dilated by large gliomatous hernias, in which there were no myelinated fibers but one could observe granular corpuscles. Undoubtedly the presence of these corpuscles was the result of degeneration of the root fibers infiltrated by the tumor.

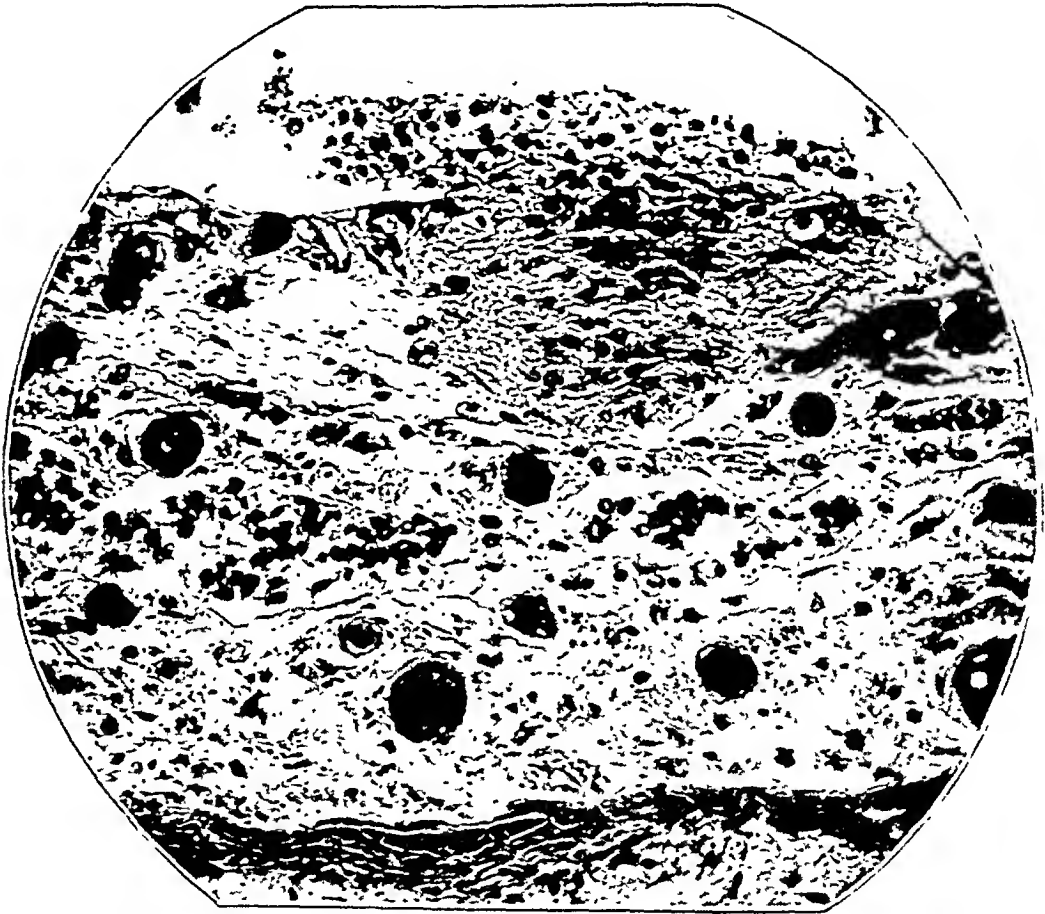


Fig. 4.—Upper thoracic region. In the lower portion of the figure is the pia mater.

The entire middle portion is occupied by the arachnoid, which contains numerous capillaries filled with red cells. In the lacunas of the arachnoid can be seen small, free cells with spherical nuclei. These nuclei are either small and dense, like lymphocytes, or large and light.

Some of the larger cells are surrounded by cytoplasm having angular outlines; they are young astrocytes.

Between these young astrocytes and the fibrillar astrocytes which form the other part of the tumor all figures of transition can be observed.

In the upper area is a fibrillar and differentiated gliomatous nodule; it is surrounded by a mass of angular or lymphocyte-like cells, being on a fair way to differentiation.

Upper Thoracic Portion of Cord: There was no neoplastic tissue in this portion of the cord. Secondary degeneration of tracts was observed. The pia mater was not ruptured but was superficially invaded. The gliomatous tissue filled less and less the subarachnoid space as it reached the cervical region, where the glioma was exclusively meningeal. The growth had a reticular structure (type 2); it was very cellular and little fibrillar. Here and there, the third structural type of the tumor could be seen: in the narrow spaces of the arachnoid near the pia, in the interstices of the pia mater and in the dentate ligament (fig. 4). Tissue of type 3 was made up of perfectly round cells; some very small and lymphocyte-like; others, larger with a dense nucleus, which was surrounded by a basophilic and homogeneous cytoplasm. These cells infiltrated the interstices of collagen tissue; they were scattered, or gathered together or arranged in rows. In some of these groups one could see some cells with angular and less dense cytoplasm and others which were decidedly branched and fibrillar. All intermediate forms between the undifferentiated, globular cells and the purely glial and reticular bands of cellular elements could be seen.

Condition of the Cord.—In the lumbar region nothing remained of the cord. In the lower thoracic region one could identify rare nerve cells in stages of degeneration amid the glial tissue and numerous granular corpuscles in the area of the neoplasm subjacent to the pia. In the upper thoracic region there was complete degeneration (Marchi-scarlet red stain) of the Goll, Flechsig, Gowers and spinothalamic tracts. The pyramidal and laterolateral tracts were normal.

Roots: Lumbar region: The anterior roots were embedded, but normal; the posterior roots were partially infiltrated.

Lower thoracic region: The anterior roots were fibrous and embedded; in the posterior roots the areas of emergence were invaded; the roots themselves were embedded but intact.

Upper thoracic region: All the roots were embedded but not infiltrated. In the posterior roots some figures of wallerian degeneration were noted.

COMMENT

Pathologic Observations.—This tumor is interesting from many angles: its intramedullary origin and its large volume; its notable extension to the leptomeninges and even the dura, which was locally destroyed, and its predominant structure, which was that of a fibrillar astrocytoma. We noted the mature neuroglia cells in the meninges and the continuity of the intramedullary and the intrameningeal glial tissue in the caudal region of the tumor; so we concluded that we were dealing with a case of simultaneous medullary and meningeal gliosis. But we now reject that hypothesis: The associated gliosis of the meninges and the nerve tissue is a congenital malformation, not a tumor process. The volume of the glial growth in our case, which took the place of the tissue of the cord and invaded the meninges, led us to believe that it was a neoplastic process and that the neoplasm was malignant. But two facts, apparently incompatible, had to be conciliated: the nature and structure of the neoplastic tissue, which was that of a glioma usually confined to the neuraxis, and its diffusion into the meninges. Meningeal gliomatosis secondary to intracranial tumor is frequent, and the gliomatosis origi-

nating in intramedullary neoplasm is rare. One wonders whether that rarity is not more absolute than relative and whether it is not due chiefly to the histologic type of the medullary tumors and to their infrequent occurrence. The majority of the encephalic gliomas which invade the meninges are medulloblastomas. Theoretically, the medulloblastoma arises only in the cerebellum, since medulloblasts are to be seen exclusively in the cerebellum (Kershman). Thus the cord cannot give rise to the type of neoplasm which is the most likely to invade the meninges. Therefore only the histologic types similar to the intracranial gliomas which do not or very seldom invade the meninges are observed in the cord.

One can easily explain the paradox of the expansive tendency of the tumor and its astrocytic and fibrillar structure. As has been stated, the tumor did not invade the meninges by means of its astrocytic components, but by cells which were free and undifferentiated. One could qualify them as lymphocytes, medulloblasts or apolar glioblasts; it was their maturation in situ and their transformation into astrocytes which indicate their glial nature. The same phenomenon occurred here as in cancer of other tissues. In the case of epidermal carcinoma, for instance, invasion is executed by undifferentiated cellular elements. It is only when those undifferentiated cells have set themselves in the connective tissue, only after their multiplication in situ, that they become differentiated, malpighian and corneous.

The differentiated cells permit one to determine precisely the nature and origin of the tumor, but they are not the active and aggressive elements of the neoplasm. In short, if a tumor in its older parts is a typical fibrillar astrocytoma, with mature and quiescent elements, its malignancy depends on the undifferentiated cells which infiltrate the meninges, like the cancerous cells.

Thus, the neoplasm grows by the migration of its undifferentiated cells, that is, according to a process of extension. It grows also by the multiplication in situ, in conquered soil, of the same cells, i. e., by a process of expansion; these cells become mature and increase at the same time their mass and their fibrillar apparatus. It is probable that the process of infiltration by the free cells, which could be observed in the upper thoracic meninges, had been going on since the onset of evolution of the tumor. Those cells were the malignant elements of the glioma, and the prodigious diffusion in the meninges and the roots was due to their activity.

What should be the denomination of the tumor? To designate it, as is frequently done, according to the prevalent cellular configuration, that is, as a fibrillar astrocytoma, would be orthodox, but it would not be precise with regard to the aggressive character of this tumor. On account

of the polymorphic and malignant character of the glioma, it could be named glioblastoma multiforme, as Eden was tempted to do in the case of a similar tumor he recently reported. But the denomination would, again, be incorrect. In the glioblastoma multiforme all sizes of cells are anarchically arranged; besides, this type of glioma is distinguished chiefly by atypical and monstrous glia cells and by telangiectatic and proliferating vessels. Nothing of the kind was noted in our glioma: The invading cells were not atypical or monstrous; they were undifferentiated, and the multiple forms of the "installed" cells represented the successive stages of their astrocytic maturation; moreover, the vessels were almost rectilinear and without any endothelial mitosis.

We believe that in the case of this tumor, as in that of every tumor of the central nervous system, one should designate the neoplasm by a name which refers primarily to the cellular element of origin and secondarily to the degree of maturation reached by the descendants of that element. The name "malignant glioblastoma with astrocytic evolution" is the only one which sums up the morphologic and evolutive characters of our tumor.

Clinical Observations.—The survey of the observations published in cases of gliomatosis arising from an intramedullary tumor and the clinical study of our case show that the signs of an intracranial pressure syndrome are usually the first and the obvious clinical indication of the neoplastic invasion of the meninges. One wonders why the neoplastic metastasis in the meninges does not more often produce radicular pains, meningeal irritation and signs of motor inhibition.

If one does not know that an intramedullary glioma can invade the leptomeninges, one is likely to miss the diagnosis of secondary gliomatosis, even if there are signs of intracranial pressure. However, in some cases of meningeal metastasis from an intracranial glioma, root pains, signs of meningeal irritation and absence of some tendon reflexes were observed. But meningoradicular manifestations can more easily be elicited from patients having a normal cord than from those who have a medullary tumor producing neurologic signs over the limbs and trunk before the appearance of any complication. Most often one observes, without any definite transition, signs which indicate an intracranial lesion, such as intracranial pressure syndrome or paralysis of some of the cranial nerves. The asymmetry of the pupils reported in older observations must be regarded as a sign of such intracranial extension of the gliomatous process.

Firor and Ford¹⁸ emphasized the frequency of functional disturbances of the eighth cranial nerve, and even of paralysis of some

18. Firor, N. M., and Ford, F. R.: Gliomatosis of the Leptomeninges, *Bull. Johns Hopkins Hosp.* 35:108 (April) 1924.

other cranial nerves. But the important paper of Ford and Firor,¹⁹ containing 4 personal observations and a résumé of 28 others collected from the literature, referred to the meningeal infiltration from intracranial tumors; in only 1 case was the primary location of the neoplasm in the cord. The invasion of the intracranial meninges in those cases was more rapid and severe, and this fact may explain the higher incidence of paralysis of some cranial nerves.

The intracranial pressure was doubtless due to the block in the cisterns at the base of the brain and to the decreased absorption of the fluid into the venous sinuses. One might also wonder whether the severe infiltration of the spinal meninges would not increase the intracranial pressure by the mechanism of eliminating the spinal circulation, and even absorption of the fluid. That is not probable in cases of high spinal block, caused by tumor, for instance, which does not obviously modify the intracranial pressure. Moreover, the meningeal invasion by the neoplasm, as was observed in our case (after the operation), does not systematically block the spinal subarachnoid space, and even then intracranial pressure can be maintained. The intracranial pressure syndrome of our patient was the result of extension of the gliomatosis toward the brain. Verdun,³ who made an important contribution to the study of gliomatosis of the meninges, diagnosed the secondary meningeal invasion in a case of cerebral glioma by discovering neoplastic cells in the fluid. This diagnostic procedure can be used with a greater accuracy since Forster¹⁷ has described a precise method of identifying the neoplastic cells in the fluid. By this means one can assert with conviction that the gliomatous process has already invaded the meninges, before any clinical signs or symptoms can be elicited.

In some cases the operation facilitates the meningeal invasion. But we must emphasize that in our case the infiltration existed before the surgical exploration.

SUMMARY

Whatever the appearance of an intramedullary glioma by which its embryonic age can be assumed, the glial neoplasm is exceptionally capable, after a few months of apparent evolution, of invading the leptomeninges and of extending toward the encephalon, where it produces an intracranial pressure syndrome and neurologic signs of cranial nerve lesions.

A typical case of meningeal gliomatosis is reported.

Prof. Pierre Masson made available to me the drawing, the photomicrographs and his pathologic observations in this case and advised me with regard to the pathologic study.

454 Est, Rue Sherbrooke.

19. Ford, F. R., and Firor, N. W.: Primary "Sarcomatosis" of the Leptomeninges, *Bull. Johns Hopkins Hosp.* 35:65 (March) 1924.

SEQUELS OF EQUINE ENCEPHALOMYELITIS

H. H. NORAN, M.D.

AND

A. B. BAKER, M.D.

MINNEAPOLIS

Whenever a new disease of the nervous system is identified, one of the most commonly used criteria of its seriousness is the fatality rate in a large series of cases. This is by no means the best measure of the resulting damage, since even in cases of recovery there may occur physical and mental residuals which in themselves may be as disastrous as the fatalities. However, in order adequately to evaluate such sequelae, it becomes necessary to follow a large number of cases over a period of years. Such a study has, as yet, not been attempted for equine encephalomyelitis, since the actual recognition of this disease in man has been relatively recent. Even its absolute identification in horses did not occur until 1931, when Meyer and his co-workers¹ isolated a virus as the etiologic agent. Since the recognition of the equine virus and the discovery that neutralizing antibodies appear in the serums of convalescing and recovered patients, much progress has been made in the clinical identification of this illness in man. It has become increasingly apparent that this disease is indeed widespread throughout the United States and Canada. The western variety particularly has been prevalent in the midwestern states for many years, and its incidence has been increasing at an amazing rate. In the summer of 1941 an outbreak of the disease in man produced one of the largest local epidemics known in the United States. The mortality rate in this epidemic was not high, varying between 10 to 15 per cent, as compared with 75 to 90 per cent reported for the eastern variety of the disease. This mortality rate, however, does not necessarily offer a true evaluation of the gravity of the illness, since residuals may make the outlook even in the cases of recovery much more guarded and less optimistic. That actual damage to the brain does occur during the acute stages of even the milder western variety of this disease has been proved beyond a doubt by some of the more recent

From the Division of Nervous and Mental Diseases, University of Minnesota.

This study was aided by a grant from the Research Funds of the Graduate School of the University of Minnesota.

1. Meyer, K. F.; Haring, C. M., and Howitt, B. F.: The Etiology of Epizootic Encephalitis of Horses in the San Joaquin Valley, 1930, *Science* **74**:227, 1931.

publications (Baker and Noran,² Weil and Breslich³). Lesions appear throughout the nervous system and consist of focal, diffuse and perivascular infiltrations of polymorphonuclear leukocytes and mononuclears, vascular thrombi and endothelial proliferation with vascular occlusion, as well as scattered areas of demyelination. The destruction of myelin is often complete, with the formation of softened areas filled with scavenger cells or of actual cysts. Petechiae occasionally are present and are of sufficient magnitude to result in destruction of tissue. In cases of the eastern variety the lesions are reported as being somewhat similar but more severe, with greater injury to nerve cells and less alteration of myelin (Wesselhoeft⁴ and Farber⁵ and their associates).

Although the pathologic changes so far reported have been based on cases in which death took place during the acute phase of the illness, it is logical to assume that similar lesions, even though less severe, must occur in some cases in which there is apparent recovery. One feels justified, therefore, in predicting that in some such cases cerebral damage of a temporary, or even permanent, nature must result. If these alterations are progressive or involve important functional areas of the nervous system, definite clinical changes of a physical or mental nature will eventuate. The less obvious sequels, naturally, will be overlooked unless careful follow-up examinations are undertaken, but the more dramatic residuals should certainly begin to attract attention. That permanent cerebral damage with sequels does occur in cases of equine encephalomyelitis is now beginning to be apparent from a review of the literature. It is becoming obvious that at least in children both strains of the virus may and do cause permanent and disastrous after-effects. Howitt,⁶ in 1939, reported 29 cases in which there was a history of encephalitis and the serum contained neutralizing antibodies against the western strain of equine encephalitis. In all but 1 of these cases recovery occurred, and in 3 there were permanent residuals. In 2 cases the nature

2. Baker, A. B., and Noran, H. H.: Western Variety of Equine Encephalitis in Man, *Arch. Neurol. & Psychiat.* **47**:565 (April) 1942.

3. Weil, A., and Breslich, P. J.: Histopathology of the Central Nervous System in the North Dakota Epidemic Encephalitis, *J. Neuropath. & Exper. Neurol.* **1**:49, 1942.

4. Wesselhoeft, C.; Smith, E. C., and Branch, C. F.: Human Encephalitis: Eight Fatal Cases, with Four Due to the Virus of Equine Encephalomyelitis, *J. A. M. A.* **111**:1735 (Nov. 5) 1938.

5. Farber, S.; Hill, A.; Connerly, M. L., and Dingle, J. H.: Encephalitis in Infants and Children Caused by the Virus of the Eastern Variety of Equine Encephalitis, *J. A. M. A.* **114**:1725 (May 4) 1940.

6. Howitt, B. F.: Viruses of Equine and of St. Louis Encephalitis in Relationship to Human Infections in California 1937-1938, *Am. J. Pub. Health* **29**: 1083, 1939.

of the residuals was not described, while in the third, two months after apparent recovery, persistent convulsions developed. Davis⁷ recorded 2 cases in which western equine encephalitis had permanent residuals. In his first case, that of an infant 2½ months of age, two months after recovery from the acute illness, apparent blindness, deafness, mental deterioration and cerebral atrophy, suggested by the overlapping of the cranial bones, were noted. In the second case, that of a 3 month old infant, left-sided paralysis developed during the acute illness. The left arm remained spastic, and mental development was retarded. Four years later the child could speak only single words and had an intelligence quotient of 30. Convulsions had continued at the rate of two to three yearly. Samples of the blood at this time still showed neutralizing antibodies against the western equine virus. Wynns and Hawley,⁸ in reviewing an epidemic of encephalitis in California involving 102 persons, described varying sequels which were present within six months after the onset of illness. In 6 cases the complaint was weakness and inability to carry on vigorous work; in 4, neuritic pains in the limbs; in 2, persisting headaches; in 1, impairment of memory, and in 1, internal hydrocephalus. Although in these cases the equine virus was never absolutely identified as the cause, chiefly because the epidemic occurred in 1937, prior to the discovery of the etiologic agent, the nature of the illness and its regional occurrence suggest that the disease was of the western equine variety. Farber and his associates⁵ reported a study of 8 infants and children who were ill with the eastern strain of equine encephalomyelitis. In all cases the infection was identified by isolation of the virus, by neutralization tests of the blood or by pathologic examination. Of the 8 patients, 5 died and 3 recovered. All the children who recovered showed alarming residuals, suggesting extreme damage to the nervous system. The first patient, a 1 month old girl, after a coma of twenty-one days, still presented spasticity of all limbs at the time of discharge, forty days later. An encephalogram obtained after three months revealed pronounced dilatation of the ventricles. Six months later the child appeared to be mentally retarded. The second patient, an 18 month old girl, had convulsions and paralysis involving the right side. An encephalogram made three and a half months later showed moderate ventricular enlargement, the child manifesting clinically right spastic hemiplegia, partial deafness, impairment of vision and mental retardation. The case of the third patient was similar to

7. Davis, J. H.: Equine Encephalomyelitis (Western Type) in Children, *J. Pediat.* **16**:591, 1940.

8. Wynns, H. L., and Hawley, C. J.: Epidemiology of Epidemic Encephalitis in California, *Am. J. Pub. Health* **29**:781, 1939.

that of the second, and two months after recovery right-sided paralysis, speech difficulty and beginning hydrocephalus were still manifest.

Platou⁹ described in detail his observations in a case of western equine encephalitis occurring in a 5 month old male infant. During the three years following recovery from the acute illness, there developed convulsive seizures, spasticity of all limbs, atrophy of the optic nerves, mental retardation and progressive cerebral atrophy. The child finally died at the age of 3 years and 10 months. Through permission of Dr. R. V. Platou and Dr. E. J. Engberg we have had the opportunity of studying the pathologic changes within the nervous system, and these studies form the basis of the present report. The observations are of significance, since to our knowledge they represent the first report on the chronic end results of infection with the western strain of equine encephalitis. That similar, but less severe, changes occur in other cases is to be expected when one considers the great similarity of the pathologic picture in cases of acute death from this disease.

REPORT OF A CASE

History.—The history has been described in a previous publication by Platou⁹ and will be only briefly summarized at this time. A white male infant had been normal until the age of 4 weeks, when there suddenly developed high fever, strabismus and extreme irritability. The temperature remained high for one week, and convulsions appeared. Recovery occurred in ten days. After two months the infant again began to manifest convulsive seizures of increasing severity with spasticity of all limbs. Laboratory studies at this time revealed nothing abnormal, but the blood serum showed a high neutralizing titer against the western equine virus. An encephalogram showed moderate dilatation of the ventricular system with slight widening of the subarachnoid space. Convulsions continued in spite of heavy sedation, and because of the extreme mental retardation, the child was committed to the School for the Feebleminded at Faribault, Minn. Here the course was rapidly downhill. There developed almost continuous opisthotonos and spasticity of all limbs, and the child died three and a half years after the onset of his acute illness.

Gross Pathologic Examination.—A complete autopsy was performed. The significant observations were confined to the central nervous system. Externally, the brain measured 12 cm. in length and 12 cm. in width. The cerebral tissues in both frontal regions were greatly altered and were so thin as to be almost transparent. The greatest involvement occurred on the right side, where the destruction of tissue extended posteriorly to a point just anterior to the fissure of Rolando and inferiorly to the sylvian fissure (fig. 1). The adjacent temporal lobe appeared grossly intact. On the left side the involvement was much less extensive and appeared to be confined to the medial surface of the frontal lobe, covering only the superior frontal gyrus. The rest of the brain appeared intact on external examination.

9. Platou, R. V.: Equine Encephalomyelitis in Infancy, *Am. J. Dis. Child.* 60:1155 (Nov.) 1940.

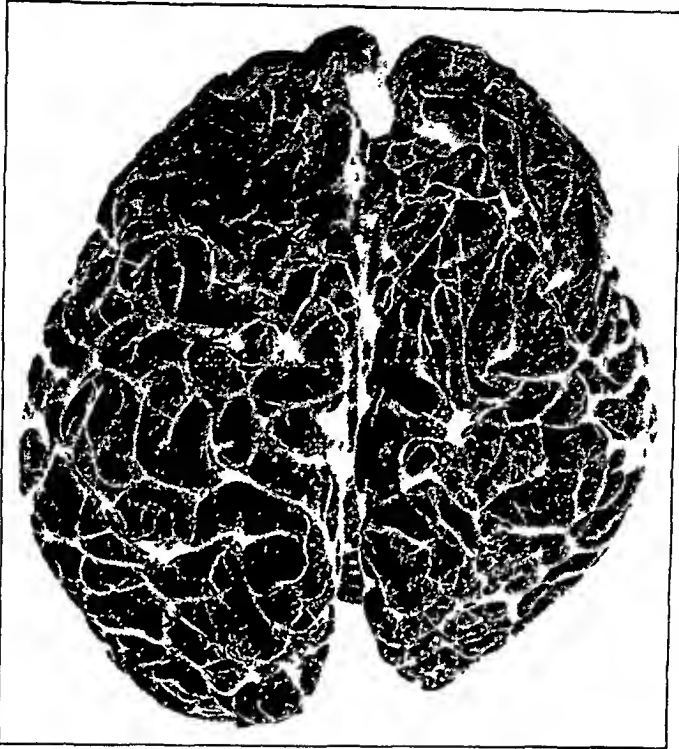


Fig. 1.—Superior view of the cerebral vertex, showing the extensive involvement of the frontal lobes. The normal convoluted pattern is largely converted into a semiopaque membrane of cerebral cortex.

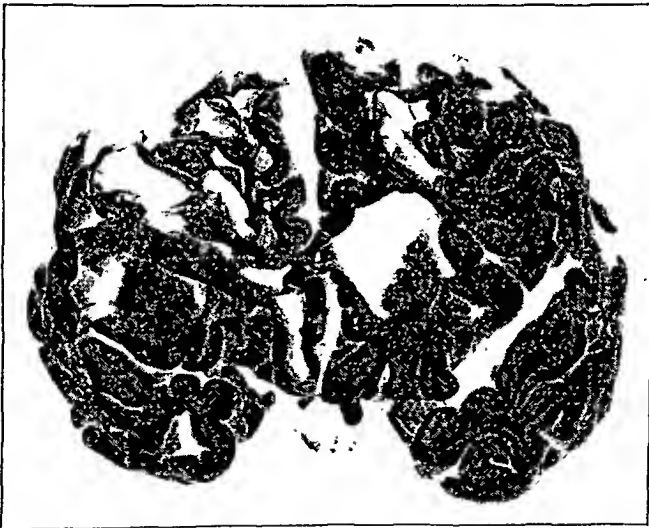


Fig. 2.—Multiple cystic areas replacing a large portion of the frontal lobes. The anterior horn on the right is dilated, while that on the left communicates with one of the cystic cavities. Note the profound destruction of the white substance and the thinning of the cortex.

Coronal sections revealed a curious alteration of the brain tissue within the frontal regions (fig. 2). The entire right frontal lobe was completely replaced by numerous thin-walled cysts. This area of cystic degeneration extended anteriorly to the frontal pole and measured 6 by 4.5 cm. in the midfrontal region at the level of the anterior border of the corpus striatum. Posteriorly the cystic areas became more circumscribed and were limited to the midportions of the medial and superior frontal gyri, terminating almost at the fissure of Rolando. These cystic alterations extended above the anterior horn and body of the right lateral ventricle but did not involve either the ventricle or the basal nuclei. Medially there still remained a thin layer of recognizable brain tissue, situated along the medial surface of the superior frontal gyrus, while laterally only a thin transparent tissue separated the destroyed brain from its overlying membranes. In the left cerebral hemisphere the cystic degeneration was much less extensive (fig. 2). It also began at the tip of the frontal lobe and extended posteriorly for 7 cm., involving primarily the midportion of the superior frontal gyrus, where it destroyed most of the cortex, only a thin, semiopaque membrane being left between the brain and the meninges. The frontal horn of the left lateral ventricle was directly incorporated in this cystic degeneration, which had broken through into the ventricle. The body of the left lateral ventricle was moderately enlarged, probably because of the shrinkage of the surrounding tissues. The middle and inferior frontal gyri, as well as the basal nuclei, on the left appeared grossly uninvolved.

The corpus callosum was greatly narrowed throughout its entire extent, the degree of thinning varying with the amount of alteration of adjacent brain tissue. In the region of the genu, where the tissue damage was most extensive, the corpus callosum was almost completely destroyed and was represented merely by a thin, semiopaque remnant, measuring 1 mm. in thickness. There were also marked thinning and partial obliteration of the septum pellucidum in this region. The columns of the fornix appeared intact. More posteriorly, at the level of the fissure of Rolando and posterior to the regions of the gross tissue damage, the corpus callosum increased in thickness.

The temporal and occipital lobes and the left parietal region appeared grossly intact. No lesions were detected in the cerebellum, pons, medulla or cord. The larger cerebral vessels were uninvolved.

Microscopic Examination.—Blocks taken from areas throughout the nervous system were prepared for study by the following technics: hematoxylin and phloxine stain, Nissl's stain (thionine), Holzer's stain, Wilder's glial stain, Bodian's stain for axons, the Turnbull blue method for hemosiderin, Von Kossa's method for calcium, Pal-Weigert's stain for myelin sheaths, Weil's method for myelin sheaths, Cajal's gold chloride-mercury bichloride impregnation method for astrocytes, Hortega's silver carbonate method for oligodendroglia and microglia and sudan III.

Frontal Region: The frontal lobes presented a similar histologic picture. They were filled with cavities of varying sizes, the walls of which for the most part were lined by fibrous glial tissue (fig. 3A). An occasional cyst appeared to be limited by relatively normal-appearing parenchyma. In general the larger cavities were empty, while a number of the smaller ones contained scavenger cells, some of which were filled with granular blood pigment. Many of these cysts were separated from one another merely by a thin band of gliotic brain tissue. A number of the cysts had extended into and had replaced the inner portion of the overlying cortex, almost extending to the surface of the brain. Here only a thin rim of gray matter separated the cavitations from the sub-

arachnoid space. This limiting rim of cortex showed complete destruction of ganglion cells and nerve fibers, with replacement of much of the tissue by a dense glial proliferation, which in places had resulted in a relatively acellular scar



Fig. 3.—*A*, two cystic areas separated by a thin band of cerebral tissue. The overlying cortex is thin and demonstrates absence of its normal cytoarchitecture. There is diffuse demyelination. Pal-Weigert stain.

B, thin rim of cerebral cortex, with complete devastation of ganglion cells. There is moderate proliferation of macroglia. Note the perivascular sheath of calcification involving two small cortical vessels toward the left of the field. Hematoxylin and phloxine stain.

(fig. 3 *B*). The rest of the frontal cortex also showed most severe, although patchy, damage to the nerve cells. The gray matter adjacent to the more severely damaged and cystic areas presented rather severe devastation of its neurons, limited

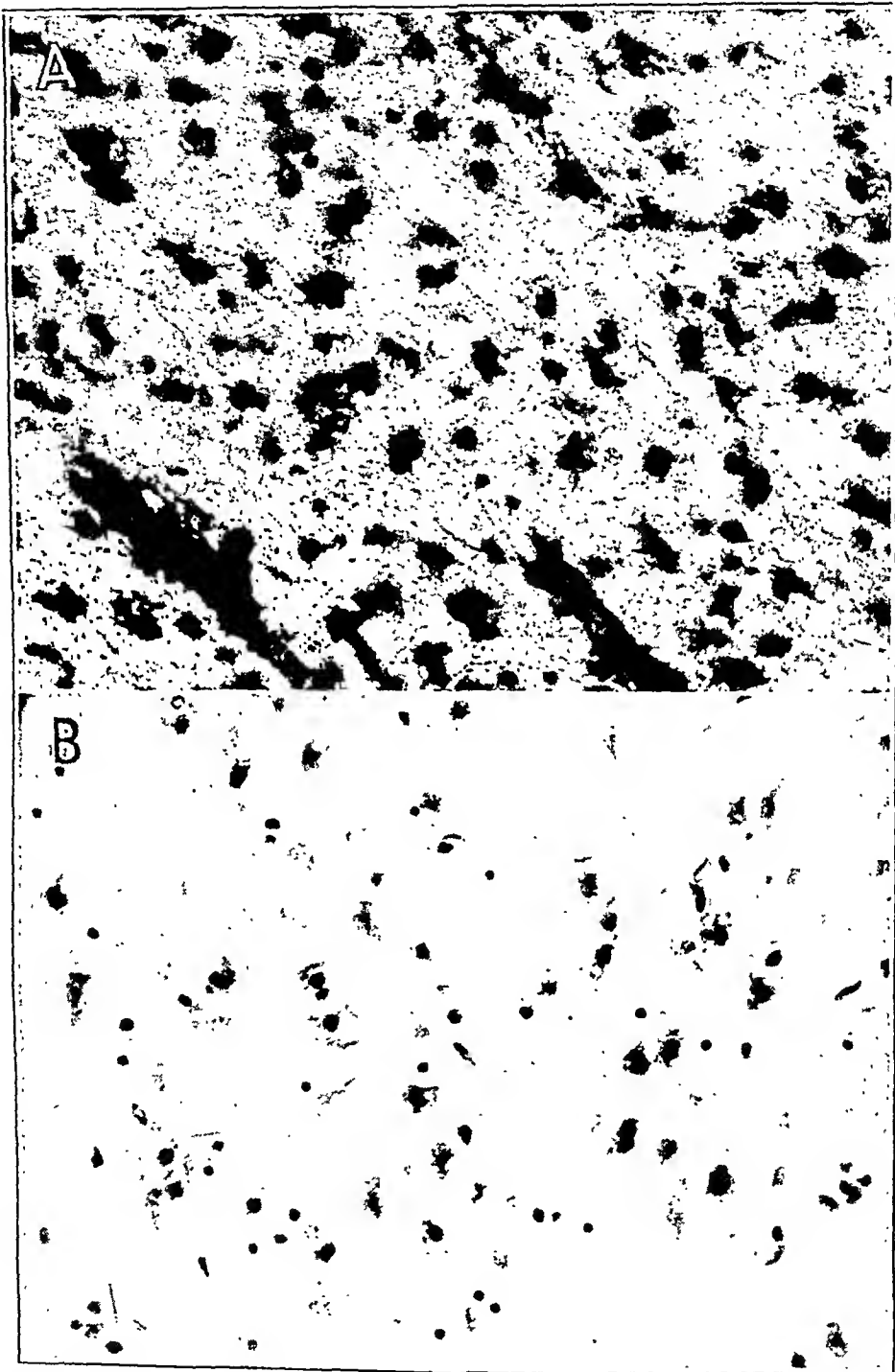


Fig. 4.—*A*, striking proliferation of astrocytes. Note the extreme cellularity, without a notable increase of neuroglial fibers. Cajal's gold chloride-mercury bichloride impregnation method.

B, disturbed polarity and lamination of the neurocellular architecture with severe structural alterations of the individual neuron cells. Ghost cell formation is prominent. Nissl stain.

primarily to its inner three layers. These areas of devastation were usually replaced by diffuse proliferation of fibrous neuroglia, although they occasionally appeared as foci of structureless, acellular tissue (fig. 4A). The cortex overlying the less severely involved frontal tissues appeared more intact. Here there occurred only patchy involvement of the neurons. Many of the nerve cells were shrunken and pyknotic with an alteration in their polarity, and others were swollen and chromatolytic, with a few cytoplasmic vacuoles (fig. 4B). An occasional ghost cell could be observed. In many cells the neurofibrils were fragmented or had undergone complete dissolution. In most areas containing the more severely damaged elements there had occurred definite astrocytic proliferation. In scattered regions throughout the involved gray matter there also appeared a slight proliferation of microglia and rod cells. Fat granule cells were absent.

The white matter adjacent to the more extensive areas of cavitation showed diffuse demyelination with complete destruction of axis-cylinders. Many of these areas of demyelination were already replaced by a relatively complete glial reaction. In the lesser involved regions of the frontal lobes there also occurred diffuse but irregular and less severe involvement of myelin, manifesting itself merely as partial loss of tinctorial properties with beginning swelling of the myelin sheaths and formation of vacuoles. The axons frequently showed irregular swellings, tortuosity and occasional fragmentation.

Throughout the frontal lobes mild vascular congestion was seen, but there were no petechiae. Particularly within the cortical gray matter the small vessels showed relatively pronounced proliferation of the lining endothelium, which had in some vessels resulted in a variable degree of attenuation of the lumen (fig. 5A). Moreover, the walls of many of these small vessels were thickened and hyaline. Thrombus formation was not observed. Small collections of basophilic granules were encountered throughout the frontal regions. These granules stained only weakly for iron but strongly for calcium. They frequently encircled small blood vessels, producing a perivascular beading and in many instances actual solid perivascular collars. In some areas they replaced the entire vessel, even extending inward to result in complete occlusion of the lumen and forming a spherical structure consisting of concentric layers of basophilic material. In certain regions the calcium granules occurred free in the parenchyma or even appeared to fill a few of the astrocytes and neurons. The degree of tissue calcification showed a definite tendency to parallel the severity of the destructive process.

Temporoparietal Region: No large cavitations were observed grossly in these areas. The cortical nerve cells, nevertheless, were severely involved, especially in the third and fourth cortical laminas on the right and in the inner three laminas on the left. In these regions, interspersed among relatively intact nerve cells, were many cells which were either shrunken and pyknotic or swollen and chromatolytic. There were also scattered areas of devastation of nerve cells situated chiefly around vessels that had undergone severe endothelial hyperplasia with occlusion of the lumen. Throughout most of the cortex appeared a mild proliferation of astrocytes. In a few locations there were a slight proliferation of microglia and a few rod cells. The white substance revealed diffuse, irregular demyelination, which extended up to the gray matter but spared the U fibers (5B). In addition there were a few perivascular foci of demyelination, some of which had resulted in small cystic areas, containing occasional scavenger cells. Throughout the diffuse areas of involvement a concurrent glial reaction had taken place.

Vascular congestion was extreme and was associated with a few small perivascular extravasations of blood. Small foci of calcium granules were also present. These were arranged chiefly along the adventitia of small vessels in a

manner similar to that in the frontal lobes. In the adventitia of several medium-sized vessels a few mononuclears and granulocytes were discovered, but no actual perivascular inflammatory infiltrates were observed.

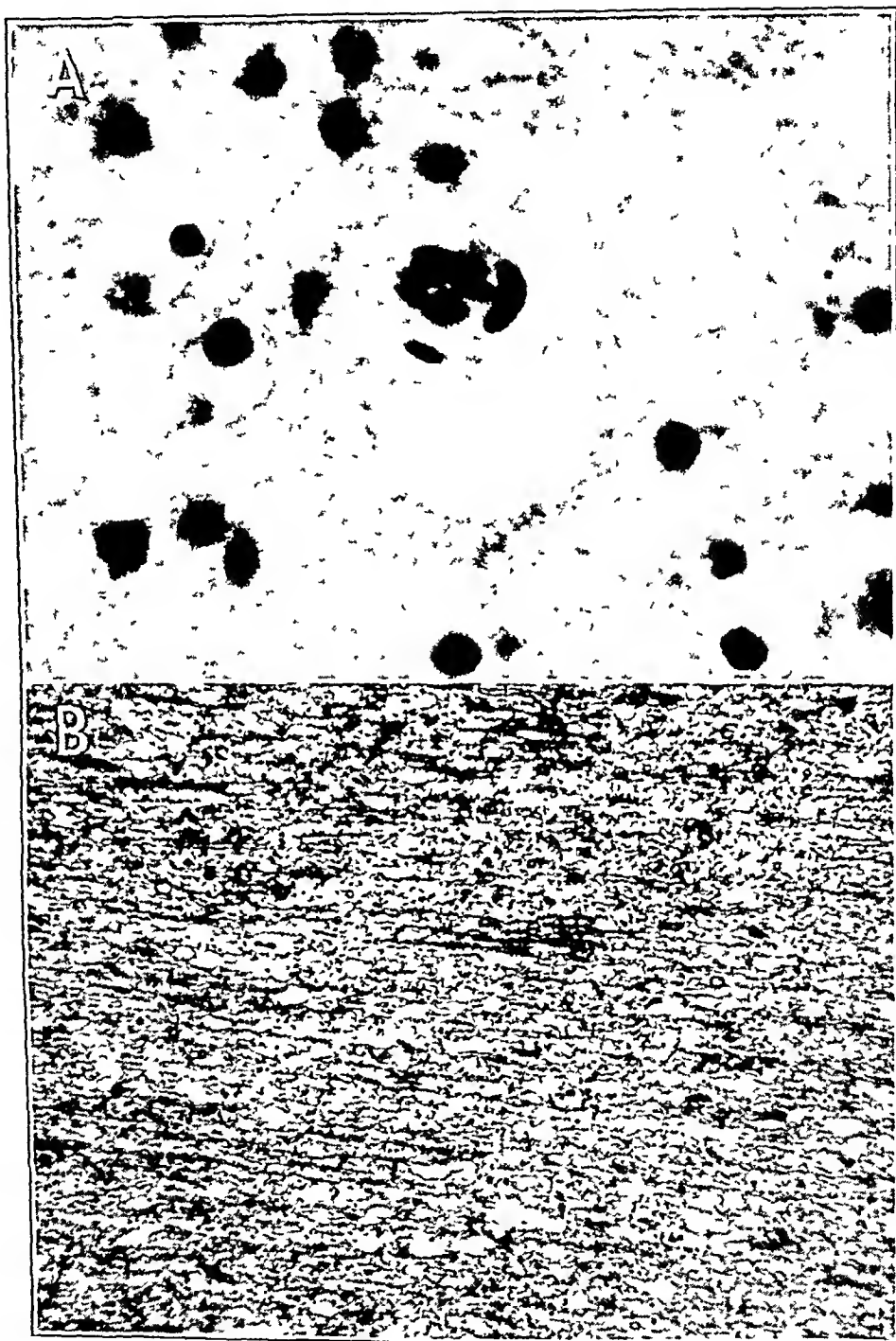


Fig. 5.—*A*, small cortical vessel displaying endothelial hyperplasia and resultant attenuation of the lumen. Hematoxylin and phloxine stain.

B, diffuse, partial myelin degeneration in the white matter. The remaining myelin sheaths manifest degenerative alterations. Pal-Weigert stain.

Occipital Region: The alterations in the occipital lobes were similar to those seen in the temporal and parietal lobes but were less extensive. Structural altera-

tions in the ganglion cells were minimal on the left but somewhat more pronounced on the right. They consisted only of scattered changes in individual cells, chiefly shrinkage and pyknosis. These changes were most evident in the second,

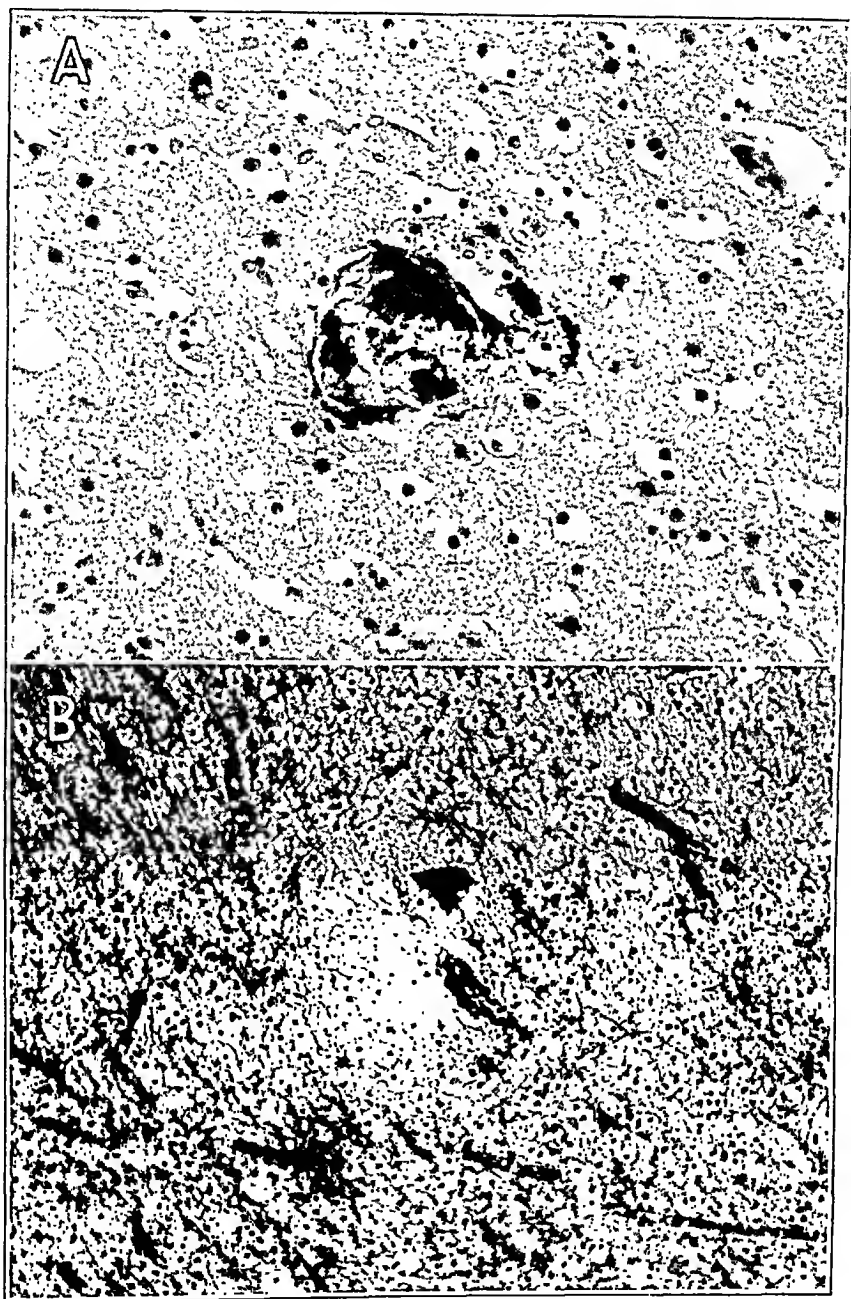


Fig. 6.—*A*, complete calcification and occlusion of the lumen of a small cerebral blood vessel. Concentric layers of calcification can be identified. Von Kossa method for calcium.

B, small focal area of demyelination. Note its perivascular location. Weil stain.

third and fourth laminae. A few small areas of perivascular destruction of nerve cells could be detected. In the outer and middle layers of the cortex of the right occipital lobe there were numerous elliptic masses of calcium, representing calcification within the walls of small blood vessels (fig. 6A). Many of the cortical vessels showed mild proliferative endarteritis, with calcium granules deposited along the adventitia of a few vessels to form thin perivascular sheaths.

Throughout the subcortical regions there were irregular, diffuse areas of demyelination, ranging from slight loss of staining properties to partial degeneration of the myelin sheaths, associated with mild to moderate astrocytic prolifera-

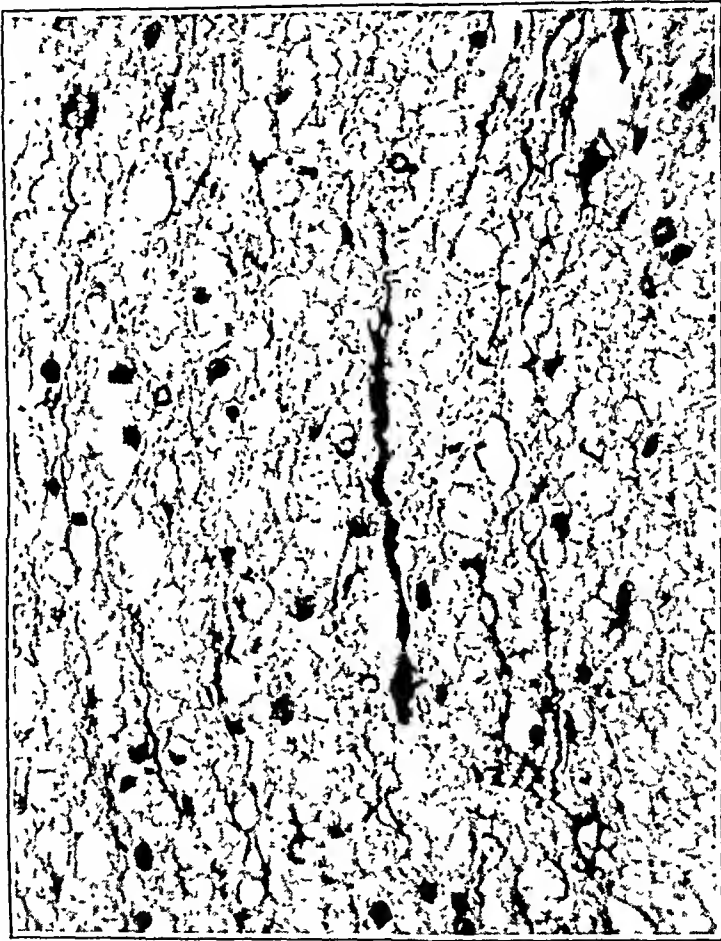


Fig. 7.—Section of the corpus callosum, revealing almost complete destruction of axis-cylinders. One of the remaining axons discloses irregularity, swelling and early fragmentation. Bodian stain.

tion (fig. 6B). The axis-cylinders were usually intact but in scattered areas showed mild degenerative changes.

Corpus Callosum: The corpus callosum had undergone extensive degeneration, especially in its anterior portion, including the genu, resulting in pronounced thinning of this structure. Only a few axis-cylinders could be identified, and these were swollen, irregular, pale and tortuous (fig. 7). There was diffuse proliferation of the fibrillary neuroglia.

Basal Ganglia: Structural alteration of the nerve cells was observed throughout the basal ganglia; however, no complete devastation had occurred. The changes consisted principally of swelling of the cell body, tigrolysis, eccentricity

and paling of the nucleus and fragmentation and dissolution of the neurofibrillae. Cells undergoing early changes revealed perinuclear chromatolysis. Occasional ganglion cells showed complete loss of their structural architecture, with resulting formation of ghost cells. Diffuse, irregular regions of severe degeneration of myelin were also present, associated with mild reparative gliosis. In a few areas the parenchyma was actually vacuolated, and the glial fibers were relatively dense. There were also a few areas of perivascular demyelination. Most of the axis-cylinders were intact; however, some disclosed moderate toxic alterations. A few mononuclears were seen in the adventitia of several vessels, but infiltration was not sufficiently marked to be regarded as unquestionable evidence of inflammation. Calcium granules were observed along the adventitia of an occasional vessel. The neurons of the insula also showed structural alterations. A few scattered foci of atrophy of nerve cells were encountered, especially in the third and fourth laminae. Many of the small blood vessels revealed proliferative endarteritis. Along the subependymal regions of the ventricles demyelination and glial repair were particularly evident.

Cerebellum: Widespread atrophy of Purkinje cells had occurred. In many of the folia few cells remained. The granular cells, on the other hand, were relatively intact. In an occasional region there did occur complete devastation of all nerve cells, including both Purkinje and granular cells. In these regions there was mild proliferation of astrocytes. The white matter of the cerebellum appeared intact. The neurons of the cerebellar nuclei were not involved.

Midbrain: The parenchymal elements, including the nucleus of the third nerve, the red nucleus and the substantia nigra, showed no noteworthy alterations. However, several petechiae were seen.

Pons: The neurons both in the tegmentum and in the nuclear region manifested mild structural changes. Some of the cell bodies were swollen and showed perinuclear chromatolysis, while others revealed minimal shrinkage and pyknosis. Only a few ghost cells were observed. The myelin and axis-cylinders showed no significant abnormalities. An occasional vessel evidenced slight endothelial proliferation.

Medulla: Structural alterations of the nerve cells were somewhat more noticeable here than elsewhere in the brain stem. Both the motor and the sensory nuclei were involved. In the olives most of the cells showed either swelling and chromatolysis or shrinkage and pyknosis. In addition, ghost cell formation was not infrequent.

The myelin showed partial destruction of its staining properties in a narrow band along the marginal zone and the subependymal region. Several petechiae were discovered in the region of the nuclei of the twelfth cranial nerves. The blood vessels, however, did not show any notable changes.

Cervical Region of Cord: The ganglion cells of the ventral horns contained only mild changes, consisting of swelling and partial chromatolysis. A few ghost cells were observed. The white substance disclosed moderate swelling of the myelin sheaths of the lateral columns and the marginal zone, but actual demyelination was not observed. The nerve rootlets showed only minimal changes. The myelin sheaths of a few fibers were swollen and showed alterations of the neurokeratin network, with resulting formation of geometric figures.

COMMENT

From a summary of the literature and a review of our case, it is obvious that the virus of equine encephalomyelitis when infecting man is capable of producing extensive destruction of tissue, resulting in

permanent and often progressive residuals. Since the actual recognition of this disease is relatively recent, it is too early to predict the frequency of such sequels. One can safely say, however, that at least in children sequelae are not uncommon and may follow infection with either the eastern or the western strain. It is interesting that the resulting symptoms and signs are remarkably similar in all the recorded cases. These consist of convulsions, muscular weakness or paralysis, intellectual deterioration and progressive destruction of tissue, as indicated by the gradual ventricular enlargement observed in air studies. Since it is known from the pathologic studies that the actual injury to tissue accompanying the acute western equine infection is not nearly as severe as that associated with the eastern variety, it seems unusual that the incidence of severe residuals should be so great. In an attempt to find an adequate explanation for this occurrence, it might be helpful briefly to consider some of the better known neurologic conditions in which lesions resemble those observed in cases of chronic equine encephalitis. Fundamentally, in our case there had occurred an extensive demyelinating process with cyst formation and secondary glial reaction. Such a pathologic picture resembles in many of its features the lesions seen in cases of cerebral anemia or of severe hypoglycemia (Döring,¹⁰ Kammy,¹¹ Gildea and Cobb,¹² Baker¹³). It is well known that vascular occlusion, regardless of the cause, will result in breakdown of the surrounding tissues, with secondary glial repair. When larger vessels are involved and the breakdown of tissue is fairly rapid, the glial elements frequently do not invade the destroyed area but proliferate about the periphery to produce a glia-lined cyst. Döring¹⁰ and Kammy¹¹ described 4 cases in which the patients died days after severe cerebral anemia. These investigators observed damage to cerebral nerve cells, vascular congestion and many areas of demyelination, which in some regions had transformed the brain into a spongy tissue. Cysts are frequently observed in the tissues of older persons, in whom cerebral arteriosclerosis with vascular occlusion is common. If such vascular occlusion were to become widespread, involving many vessels within a single lobe of the brain, it is possible to see how extensive cystic

10. Döring, G.: Cerebral Changes in Delayed Death After Hanging and Ligation of the Carotid Artery, *Virchows Arch. f. path. Anat.* **296**:666, 1936.

11. Kammy, E.: Beitrag zur Histopathologie und Histogenese der Sauerstoffmangelshädigung der Gewebe mit besonderer Berücksichtigung des Gehirns, *Beitr. z. path. Anat. u. z. allg. Path.* **100**:248, 1938.

12. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, *Arch. Neurol. & Psychiat.* **23**:876 (May) 1930.

13. Baker, A. B.: Cerebral Lesions in Hypoglycemia: II. Some Possibilities of Irrevocable Damage from Insulin Shock, *Arch. Path.* **26**:765 (Oct.) 1938; Cerebral Damage in Hypoglycemia: A Review, *Am. J. Psychiat.* **96**:109, 1939.

degeneration might result, such as occurred in our case. Hypoglycemia, which probably also results in circulatory disturbance, characteristically produces a pathologic picture similar, in some respects at least, to the lesions seen in cases of equine encephalitis. Lindsay and his co-workers¹⁴ described cystic spaces in the brain of their patient who died during a hypoglycemic reaction. In cases of hypoglycemia reported by one of us (A. B. B.) large areas of encephalomalacia, demyelination and cyst formation were frequent and constant.

The resemblance of the cerebral lesions associated with chronic equine encephalitis to those seen in cases of cerebral anemia and hypoglycemia suggests the possibility that the changes resulting in the equine infection might well be on a vascular basis. When one considers the vascular changes occurring within the nervous system in cases both of acute and of chronic equine encephalitis, it is not difficult to accept such a suggestion. In cases of the acute form the smaller arterioles throughout the brain show swelling and proliferation of their endothelial lining, often with complete occlusion of the lumen. Occasionally these small vessels are surrounded by both polymorphonuclear leukocytes and mononuclears, which invade the vascular wall and, with secondary tissue proliferation, result in occlusion. Similar widespread proliferative endarteritis was observed in our case several years after the acute infection. It seems likely that the extensive involvement of small vessels could have resulted in localized anemia with patchy cellular and tissue damage, changes which would account for the widespread alteration of nerve cells throughout the gray matter of the nervous system. The irregularity of the cell changes certainly adds weight to such an explanation. It is more difficult to account for the extensive demyelination and cyst formation on a similar basis. However, if one again refers to the alterations reported in cases of death from the acute form, it is obvious that extensive changes also occur within the larger cerebral vessels. These vessels do not show endothelial increase but frequently contain pus cells enmeshed within the adventitia. The lumen is often filled with neutrophils, which appear as a septic thrombus completely occluding the vessel. Such involvement of the larger vessels could easily account for the extensive demyelination and cyst formation seen with the more chronic form. It is inevitable that such occlusion of large vessels should result in extensive damage to the brain, in a manner similar to that accompanying any other type of vascular thrombus. Signs of acute inflammatory reaction were entirely absent in our case, but such elements would naturally tend to disappear after the acute

14. Lindsay, J. W.; Rice, E. C.; Selinger, M. A., and Mish, K. W.: Protamine Insulin as a Contributing Factor in the Death of a Diabetic Patient with Cerebral Arteriosclerosis, *Ann. Int. Med.* **10**:1892, 1937.

illness and would probably be absent after a period of years. Therefore, when the fundamental pathology of this disease is considered, it is not difficult to account for the chronic changes, and it becomes apparent why such severe residuals might occur even in the face of a relatively mild infection, provided the vascular irritation and damage are sufficiently great. The observations certainly point to a hematogenous spread of the virus, since the fundamental damage appears to occur within the vascular structures. All the other tissue changes could well be secondary to such vascular alterations. Further evidence pointing to primary vascular damage in this disease is the extensive calcification occurring within many of the vessels. Calcification frequently follows a number of degenerative processes within the nervous system, and when present suggests some preceding tissue degeneration. No doubt in the present case the extensive vascular damage, with occlusion of the lumens and ischemia, had resulted in sufficient tissue damage to stimulate the extensive calcification observed.

SUMMARY AND CONCLUSIONS

A review of the literature demonstrates that neurologic sequels of a chronic and progressive nature may follow the acute infection in cases of equine encephalomyelitis.

A clinicopathologic study of such a case is presented. In this case, the lesions consisted chiefly of a destructive process which had produced multiple glia-lined cavities within the frontal lobes and widespread degeneration of the parenchymal elements throughout the brain. Many of the vessels were occluded by an endothelial increase or by deposition of calcium within their lumens.

The extensive vascular damage, with occlusion of the lumens and ischemia, appears to be the primary cause of the tissue damage in this disease and suggests a vascular spread of the virus.

University of Minnesota Medical School.

ATTEMPTS AT TREATMENT OF SCHIZOPHRENIA AND OTHER NONEPILEPTIC PSYCHOSES WITH DILANTIN

LOTHAR B. KALINOWSKY, M.D.

AND

TRACY J. PUTNAM, M.D.

NEW YORK

Not only is dilantin an anticonvulsant but it is capable of producing distinct changes of mood. Unlike bromides and phenobarbital, in most instances dilantin has a striking effect on psychic equivalents.¹ Blair, Bailey and McGregor² gave special attention to this action and reported that most of their epileptic patients became "more cheerful and congenial, less quarrelsome and complaining, and more easily managed." There is evidence that this effect of dilantin is independent of a decrease in the number of convulsions, whereas improvement in intelligence and performance tests seems to parallel the reduction in the number of convulsions. Ross and Jackson,³ who differentiated carefully between the effect of treatment on psychometric rating and that on conduct, mentioned a patient whose seizures were controlled by dilantin and who also exhibited remarkable improvement in behavior; when dilantin was withdrawn, he had no recurrence of convulsions, but he returned fully to his resistive manner.

In view of these results, it seemed appropriate to investigate the possibility that dilantin might also be capable of influencing mental symptoms of other origins. Such an idea seemed conceivable for another reason. Gibbs, Gibbs and Lennox⁴ were the first to demonstrate a likeness of the cortical dysrhythmia of psychomotor epilepsy to that in some cases of

From Pilgrim State Hospital, Brentwood, N. Y.; the Neurological Institute of New York, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

1. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinat in the Treatment of Convulsive Disorders, *J. A. M. A.* **111**:1068 (Sept. 17) 1938. Lennox, W. G.: The Drug Therapy of Epilepsy, *ibid.* **114**:1347 (April 6) 1940.

2. Blair, D.; Bailey, K. C., and McGregor, J. S.: Treatment of Epilepsy with Epanutin, *Lancet* **2**:363, 1939.

3. Ross, A. T., and Jackson, V.: Dilantin Sodium: Its Influence on Conduct and on Psychometric Ratings of Institutionalized Epileptics, *Ann. Int. Med.* **14**: 770, 1940.

4. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy, *Am. J. Psychiat.* **95**:255, 1938.

schizophrenia, which might indicate some relationship between the two clinical entities. These authors expressed the hope that schizophrenia might also be amenable to chemotherapy.

The present report is based on an attempt at such treatment by means of dilantin. Data on 60 cases are presented. A few remarks about the procedure are necessary. Although the large material of a state hospital was available, it seemed inadvisable to deal with a great number of patients simultaneously; consequently, no more than 4 or 5 patients were treated at a time. A special nurse was assigned to give the drug to be certain that the patient really swallowed it. All patients who took the drug irregularly were excluded from this report. Symptomatic changes, as well as final results, were closely observed. It was felt advisable to approach the toxic level as nearly as possible, as is usually done in cases of epilepsy, in order to be sure to elicit the maximum effect. For this

Symptomatic Results in Treatment of Sixty Patients with Dilantin

Syndrome	Total No.	No. Greatly Improved	No. Moderately Improved	No. Unimproved
Schizophrenia with syndrome of excitement....	22	4	12	6
Schizophrenia with catatonic stupor.....	6	0	1	5
Other forms of schizophrenia.....	13	2	3	8
Manic-depressive psychosis (manic type).....	9	5	3	1
Manic-depressive psychosis (depressed type)....	5	1	2	2
Involitional psychosis	4	1	2	1
Mental deficiency (excitement).....	1	0	0	1
Total no.	60	13	23	24

reason a careful watch for toxic symptoms was kept. The initial daily dose was usually 3 or 4 capsules of 0.1 Gm. each; after two days this dose was increased to 5, and later to 6, capsules. Sodium dilantin was used, except with the few patients who had gastric irritation with this drug; their treatment was continued with the new acid dilantin in oil. The duration of treatment was from two to five weeks in this preliminary study. None of the patients received any other special treatment during the medication with dilantin; psychotherapy and suggestive measures of all kinds were purposely omitted.

The difficulty of judging results in treatment of mental disorders is well known. We, therefore, tried to reach a better evaluation of the improvement in each patient by observing him for a short period after dilantin was discontinued, and subsequently by employing one of the shock treatments. This was done in order to see whether the patient had a chance of improvement with any of the methods of treatment at present available.

The table classifies the patients treated according to diagnosis in such a way as to give information also on what types of the various disease

entities showed responses. The results are designated as "unimproved," "moderately improved" and "greatly improved," the classification referring not to permanent results but to the condition of the patient during and at the end of the period of medication.

Forty-one patients carried the diagnosis of dementia praecox. It soon became obvious that the disturbed patients, especially those in catatonic excitement, showed by far the best response. Most patients with catatonic stupor were uninfluenced. In patients with other types of dementia praecox, especially the paranoid, the results were variable, but, again, those with the picture of excitement responded best. Hallucinations disappeared in 1 instance only. The patient in this case had vivid auditory hallucinations which troubled him considerably. They disappeared after five days of treatment with dilantin sodium in doses which were gradually increased to 0.5 Gm. daily. Treatment was discontinued two weeks later, and the hallucinations reappeared after four days. When the patient was again given dilantin, these hallucinations disappeared and did not recur as long as he was under treatment.

In the group with manic-depressive psychosis, patients with manic attacks showed by far the best results. Of 9 patients, 5 had complete disappearance of manic excitement during the medication. In 2 of these 5 patients the manic phase was followed immediately by a depression, an occurrence which is also frequent in spontaneous remissions of manic attacks, as well as in remissions following convulsive treatment. Of the remaining manic patients, all but 1 improved slightly. The depressed patients within the group with a manic-depressive psychosis and the patients with involutional psychosis showed poor results. Closer study of the few improved patients in these two groups indicates that only disturbed persons with the agitated type of depression reacted favorably.

Our experience with this group of 60 patients leads to the conclusion that the action of dilantin is not limited to a special group of psychiatric disorders, but that this drug has a purely symptomatic action on states of excitement in various psychoses. This effect is obtained in spite of almost complete lack of narcotic action. The improvement was brief in most patients after the drug was discontinued. As with epileptic patients, they maintained their improvement for one or two days after the medication was stopped. In some patients the effect was lasting as far as the disturbed phase was concerned. With several patients who relapsed, dilantin treatment was resumed again, and the improvement recurred. Such observations indicate that dilantin was responsible for the achieved symptomatic improvement. It was obvious that in schizophrenic patients the basic symptoms in the spheres of thought and affect remained untouched. However, subsequent electric shock treatment in several instances led to a remission after only one convulsion. Usually

this improvement takes place only between the fourth and the sixth convulsion. Such response to the first convulsion in electric shock treatment was seen likewise when the convulsive treatment was preceded by a course of subconvulsive responses.⁵ Systematic attempts at medication with dilantin prior to shock treatment are planned.

The resemblance of these results in the major psychoses to the effect of dilantin on mental symptoms of epileptics is striking. In both instances the patient's excitement, aggressiveness and other disturbances of behavior are influenced. The psychotic patient with dangerous tendencies becomes pleasant and cooperative. Psychomotor hyperactivity and overproductiveness are reduced to a more normal level of activity. This effect becomes noticeable only after several days of medication, and becomes distinct only when the dose approaches the toxic level. The more continuous mental changes of the "irritable" epileptic patient are influenced only as long as dilantin is given. In the same way, the excitement of the schizophrenic or the manic patient, being a more continuous symptom, will usually reappear a few days after dilantin is discontinued. It must be pointed out, however, that there were a few instances of lasting symptomatic improvement in schizophrenic patients who remained quiet after dilantin had ended the excitement phase. The change was also permanent during the period of observation in most manic-depressive patients as far as the manic phase was concerned.

Three short case reports illustrate some of the results. The first case represents the usual type of catatonic excitement, which improved only as long as dilantin was given, and the second, permanent improvement of the excitement; the third case is that of a manic patient who quieted down under dilantin but entered a depressed phase.

REPORT OF CASES

CASE 1.—A. A., a white woman aged 34, with a negative family history for mental disorders or epilepsy, had the first psychotic episode in 1925, at the age of 18. She became acutely disturbed and assaultive and was an inmate of a state hospital for five months. The second attack occurred in 1931, at the age of 24, with mood changes, paranoid trends and misidentification of those about her. She assumed bizarre postures and showed mannerisms. This attack lasted nearly one year. The present attack started in February 1941. She cried, had delusional ideas of jealousy and of reference and finally became resistive and assaultive. On admission to the Pilgrim State Hospital on April 2, 1941, she was constantly assaultive, soiled and wet herself and talked incoherently. She had to be kept in restraint most of the time.

The diagnosis was dementia praecox, catatonic type.

Medication with dilantin sodium was initiated on July 1, with 3 capsules of 0.1 Gm. each. From July 2 to July 5 she had 4 capsules, and from July 6 to

5. Kalinowsky, L.; Barrera, S. E., and Horwitz, W. A.: The "Petit Mal" Response in Electric Shock Therapy, *Am. J. Psychiat.* 98:708, 1942.

July 20, 5 capsules. Her condition remained unimproved for the first ten days and then showed a definite change. She lost all the features of her catatonic excitement and was no longer assaultive, but became quiet, cooperative and tidy. However, she remained silly and unreasonable, and her thought content was unchanged. She was kept under dilantin for ten days after the improvement began. She maintained her improvement for one week after the medication was discontinued. Then she again became excited and continued to be acutely disturbed. On August 8 a course of electric shock treatment was initiated; after the first convulsion she had a complete remission. She left the hospital on Sept. 28, 1941 and has been in excellent condition since.

CASE 2.—E. H., a white woman aged 20, with a negative family history for mental disorders or epilepsy, showed her first psychotic symptoms in 1939. She had delusions of persecution and thought that people were spying on her. She was still socially well adjusted. Early in 1941 she began to talk incoherently and became manneristic and later unmanageable. On Aug. 27, 1941 she was admitted to Pilgrim State Hospital. She presented the syndrome of catatonic dementia praecox just described. During her stay in the hospital she became acutely disturbed. When treatment with dilantin was initiated, she was so agitated that she had to be kept in continuous tubs.

From September 28 to October 20 she received 4 capsules (0.1 Gm. each) of sodium dilantin daily. After only three days of medication she became quiet and during the succeeding days lost her mannerisms and became coherent, pleasant and cooperative. She maintained this striking improvement not only during the treatment but after discontinuance of the medication. Despite this, however, she remained seclusive, showed inadequate affect and was underactive and at times hallucinated. It was for this reason that she was given a course of twenty electric convulsive treatments in November and December 1941. She had a full remission and was paroled on Jan. 25, 1942. She has been in good condition since.

CASE 3.—B. S., a white woman aged 46, with a negative family history for mental disorders and epilepsy, in 1940 became acutely disturbed, overtalkative and overactive. She was admitted to a private institution, where she improved only slightly. On May 7, 1941 she was admitted to Pilgrim State Hospital. She showed continuous psychomotor agitation, singing, dancing and screaming, and was overactive and at times assaultive. There were no delusions or hallucinations.

The diagnosis was manic-depressive psychosis, manic type.

On Aug. 18, 1941 medication with sodium dilantin was started. From August 18 to August 27 she received 4 capsules (0.1 Gm.) daily; from August 28 to August 29, 5 capsules, and from August 29 to September 2, 6 capsules. Five days after medication was started she became quiet and cooperative. During the succeeding days, while she was still receiving 4 capsules of sodium dilantin, her condition changed radically. Her facies became sad; she became mute, had to be spoon fed and was underactive. She continued in this stupor-like condition when the dose of dilantin was increased to 5 or 6 capsules. When medication was discontinued, she did not show further change but remained in a depression, which later was treated successfully with shock therapy.

It would be of interest to correlate these therapeutic results with the encephalographic features. The incidence of cerebral dysrhythmia in cases of schizophrenia has again been shown recently by Finley and

Campbell.⁶ We are unable at present to report whether or not in schizophrenic and manic patients also disappearance of an abnormal electroencephalographic rhythm parallels the clinical improvement under treatment with dilantin. Since many of our patients were disturbed and uncooperative, electroencephalographic studies were hardly possible and were, therefore, omitted in this preliminary study. From the standpoint of diagnosis it was felt that electroencephalographic records were not indispensable because only patients with disturbances representative of the various psychoses were selected for treatment. As the majority of our disturbed patients benefited from the treatment, it is difficult to believe that all of them were "epileptoid."

Comparison with other therapeutic procedures shows the striking similarity of our results to those reported in cases of prolonged sleep treatment with barbiturates. Here, also, the good responses in patients with catatonic excitement and manic attacks and the poor response in depressed patients have been clear.⁷ The original explanation offered for the effect of prolonged sleep treatment was that it induced rest of certain parts of the brain and permitted a better psychologic approach to the patient after the period of sleep. Later, however, it was found that the depth of the narcosis did not influence the results. Patients who never went into a deep sleep benefited from the treatment, and dial (diallyl barbituric acid), which produces less sleep, but more often toxic symptoms, such as ataxia, was considered superior to other drugs. This drug has also been found experimentally to possess anticonvulsant properties.⁸ More recent workers in this field concluded that the action of the so-called narcosis treatment is purely chemical.⁹

In dilantin treatment the hypnotic action can probably be disregarded. Even large doses of sodium dilantin—a patient of Aring and Rosenbaum¹⁰ is reported to have taken 40 capsules at one time—do not often lead to a noticeable soporific action. This seems to constitute a definite superiority of dilantin over narcotics such as barbiturates and scopolamine in the treatment of psychotic persons.

6. Finley, K. H., and Campbell, C. M.: Electroencephalography in Schizophrenia, *Am. J. Psychiat.* **98**:374, 1941.

7. Müller, M.: Die Dauernarkose mit flüssigem Dial bei Psychosen, speciell bei manisch-depressivem Irresein, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **107**:522, 1927.

8. Putnam, T. J., and Merritt, H. H.: Chemistry of Anticonvulsant Drugs, *Arch. Neurol. & Psychiat.* **45**:505 (March) 1941.

9. Meerloo, A. M.: On the Action of Barbituric Acid Compounds: A Contribution to the Prolonged Narcosis Treatment of Mental Symptoms, *J. Ment. Sc.* **79**:336, 1933.

10. Aring, C. D., and Rosenbaum, M.: Ingestion of Large Doses of Dilantin Sodium, *Arch. Neurol. & Psychiat.* **45**:265 (Feb.) 1941.

In addition to the practical use which this preliminary study suggests, the results seem of interest for an understanding of the action of dilantin in epilepsy. It can be concluded that the efficacy of dilantin in treatment of psychic equivalents is in no way specific for epilepsy, unless the conception of epilepsy is enormously expanded. Dilantin was first recognized as an anticonvulsant. The observations reported here demonstrate that dilantin has an effect on disturbances of mood, not only in epilepsy but in various other types of psychiatric disorders.

An increasing body of evidence is accumulating in favor of a chemical concept of both epilepsy and the major psychoses. Such a concept is supported, for example, by many recent electroencephalographic studies. Attempts at similar forms of chemical treatment for both groups of diseases possess theoretic interest and, it appears, some promise of practical results.

SUMMARY

Sixty psychotic patients, chosen as representing clear and typical instances of the more important major psychoses, were treated with dilantin in doses increased up to the point of tolerance. Improvement occurred in over half the patients during the period of treatment. It consisted usually of diminution of excitement and irritability, almost irrespective of the type of the psychosis. The patients tended to relapse when the drug was withdrawn. These results seem to justify a further study of the use of dilantin for psychotic states.

Dr. Harry J. Worthing, director of the Pilgrim State Hospital, made the patients available to us.

The dilantin was supplied by Parke, Davis & Co., Detroit.

EFFECT OF EXTREMES OF ENVIRONMENTAL CHANGE ON MAN

PRESIDENT'S ADDRESS

LEWIS J. POLLOCK, M.D.

CHICAGO

The neuropsychiatrists of the West are, I am sure, honored and delighted that they have been able to lure you from the deep reaches of the Atlantic seaboard, and they welcome you.

In 1875, one of the founders of the American Neurological Association, James Stewart Jewell, who had been elected first vice president, presided as the first president of this association, when S. Weir Mitchell, who had been elected president, was unable to attend and requested that his name be removed from the list of officers. This office Jewell held for the next four years. Jewell was the first professor of psychological medicine and nervous diseases, and later professor of nervous and mental diseases, of Northwestern University Medical School.

It is a source of gratification to me that the association is meeting within a biscuit's throw of this medical school. That I, inadvertently a successor to the chair held by Jewell, have been elected your president for this meeting evokes a feeling of gratitude of course, but, in addition, one of humility in the recognition of my unworthiness to follow in the footsteps of my great predecessors.

I never realized how inarticulate I am until I contemplated the writing of this address. I am not a philosopher, a historian or a prophet; neither have I contributed any noteworthy conception of research; in fact, what I have contributed has been looked on, by my friends in physiology, with amazement at the ununderstandable attempts to understand something.

I am going to describe, briefly, the effect on man of some of the environmental changes met with in war, to indicate my recognition that none of these alone or combined seems to be the causative factor in the war neuroses and to come to the bewildering conclusion that I do not believe the evidence and ask for further research.

As a young man, the assignments given me in the first World War made available a veritable treasure house of clinical material, which, because of my inexperience and only partial, and at times faulty, knowledge, coupled with the intolerance and brash confidence of youth,

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served, as I now see, only incompletely to teach me the lessons brought before me.

As, in retrospect, I remember the plentitude, variety and richness of this material, I become hopeful of again being permitted to study it.

Conditioned by my beloved chief, Patrick, with his love for France and wealth of memories of French neurologists, to an intense interest in hysteria, I looked forward to my experience with avidity. At the beginning I first met with hysteria in the general hospital in Atlanta, Ga., where Bowman and I rapidly made a whispering chorus sing with the aid of painful faradism.

I was steeped in it at the time when, in Limoges, by means of cathedrals, lunch and a modicum of wine, I circumvented our dear John Rhein from making an inspection of my neurologic wards in order to prevent the otherwise necessary report of disobedience to orders to transfer soldiers suffering from psychoneuroses to base hospital 117. I remember my contempt for and impatience with those who proposed a possible organic background for the development of the condition easily identified as hysteria, for Mott and his theory of carbon monoxide poisoning and for the preoccupation of Crile with methods of cutting trenches to increase the damping effect on blast; equally clearly I remember my success in dissipating the major stigmas of hysteria, tremor, tic, mutism, aphonia, paralysis and contracture. With greater clarity I remember with chagrin the punishment by painful faradism to which I subjected a soldier suffering from encephalitis lethargica, because of my failure to find objective evidence of disease to account for his inactivity and inaccessibility to current literature; my shame and enlightenment when Ramsay Hunt told me of an epidemic of encephalitis among the troops and demonstrated cases of the disease to me in his hospital.

Such memories are common to many. As I review my experience and the experience of others as reflected in the literature, I am not satisfied; in relation to what seemed self evident before, some doubts appear. It is as though one saw only the ends of the spectrum. It is not so much a question of Tweedledum and Tweedledee, of somatic and psychic, as of what happens to man under environmental changes. What are the separate results of these changes; how are they related to each other, and how do they, by a final common pathway, result in disease?

In the laboratory of war man is subjected to extremes of every known environmental change—among others, to starvation, dehydration, fatigue, sleeplessness, cold, heat, inundation, noise, vibration, compression, decompression, anoxia, acceleration, deceleration, concussion, collision, disease and psychologic dislocations.

The effects of many of these conditions were not adequately studied during the first World War, in part because of a difference in points of view. As Turner¹ said:

In the writings of the earlier observers on this subject, and in some at the present time, there is a tendency to attribute many of the phenomena of shell shock and the war neuroses to physical causes, such as concussion, fatigue, or gas poisoning, and perhaps to ignore, or at all events underestimate, the influence of the psychical factor. . . . The modern school of psycho-pathologists, on the other hand, may incline too much in the contrary direction, and claim all the symptoms of the war neuroses to be of psychogenetic origin.

That one or the other point of view militated against a complete investigation is emphasized in the statement of Myers²:

In this country, at least, we have been paying so much attention to the mental aspect of the war neuroses that a detailed examination of the accompanying bodily symptoms has been generally neglected.

What is known of the effects of fatigue, loss of sleep, fear, horror, rage and the like and concussion? How much do such changes, some reversible, some irreversible, contribute to the after-development of a disease, somatic or psychic, and what somatic changes result from psychic disorders?

FATIGUE, EXHAUSTION AND LOSS OF SLEEP

Although fatigue, muscular and general, has been studied experimentally, as produced by prolonged or severe exercise or long-continued monotonous tasks, and in industry, states of exhaustion, such as were observed in the first World War, have not been investigated. This exhaustion was the product not of muscular overactivity alone but of associated environmental changes of starvation, dehydration, loss of sleep, wounds, disease, pain and emotion.

The character of this fatigue may be illustrated by Crile's³ description, with excerpts from the statement of Dr. Gros, of the American Ambulance Corps.

After a sustained and heavy action at Mons, being overpowered by the enemy, the allied armies began the retirement which continued for nine days and nine nights. One hundred and eighty miles of marching without making camp is the story of that great retreat in which the pace was set by the enemy. Only rarely were sufficiently long halts made for the men to catch a few moments of rest.

1. Turner, W. A.: The Bradshaw Lecture on Neuroses and Psychoses of War, *Lancet* 2:613-617, 1918.

2. Myers, C. S.: A Final Contribution to the Study of Shell Shock, *Lancet* 1:51-54, 1919.

3. Crile, G. W.: A Mechanistic View of War and Peace, New York, The Macmillan Company, 1915, pp. 22 and 24.

Gros continued ³:

When the ambulances arrived at Meaux at midnight they found the town in utter darkness. Not a sound was heard in the street, not a light was seen. . . . Pushing open the door of a dilapidated school building, they found the building packed with wounded—over five hundred—with all kinds of wounds. Some were dying, some dead, but every one was in a deep sleep. Bleeding, yet asleep; legs shattered, yet asleep; abdomens and chests torn wide open, yet asleep. They were lying on the hard floor and on bits of straw. Not a groan, not a motion, not a complaint—only asleep.

That sleep is one of the fundamental protective agencies against exhaustion and is a remedy for the extreme state is vividly portrayed in Hurst's⁴ quotation from a war correspondent's report, in the *Daily Chronicle* of April 3, 1918, of men who fought continuously for six days and nights.

They were tired almost to death, and when called on to make one last effort after six days and nights of fighting and marching, many of them staggered like men who had been chloroformed, with dazed eyes and grey and drawn faces, seemingly speechless . . . at the gasp of strength. Towards the end of this fighting they had a drunken craving for sleep, and slept standing with their heads falling against the parapet. In body and brain, these men of ours were tired to the point of death. They felt like old men. Yet after a few days' rest they were young and fresh. It was almost impossible to believe they were the same men. They had washed off the dirt of battle and shaved, and the tiredness had gone out of their eyes and their youth had come back.

Many factors other than muscular overactivity and loss of sleep contributed to this state of exhaustion. Zabriskie and Brush⁵ described the physical and emotional fatigue among men "undergoing a new terrifying experience of open warfare under intense artillery fire for four days: No sleep, little food, and practically no water. The dehydration effects of these states were quite remarkable." The importance of emotional tone on the production of exhaustion is illustrated by Kennedy,⁶ who contrasted the large number of cases occurring in the ten day retreat by the British Fifth Army, from March 21, 1918, the men so fatigued that they could not stand, with the absence of cases of fatigue during the continuous victorious battle ending November 11. Despite the many agencies contributing to this type of exhaustion, one may profitably review what is known of some of them,

4. Hurst, A.: *Medical Diseases of War*, Baltimore, Williams & Wilkins Company, 1941, pp. 123-128.

5. Zabriskie, E. G., and Brush, A. L.: *Psychoneuroses in War Time*, *Psychosom. Med.* **3**:295-329, 1941.

6. Kennedy, F.: *Fatigue and Noise in Industry*, *New York State J. Med.* **36**:1927-1933, 1936.

the better to determine what remains to be learned in the cases encountered in war.

One is surprised to find so little in the literature concerning the effects of prolonged loss of sleep. Some changes in the brain, medulla or spinal cord have been observed. Thus, Okazaki⁷ noted alterations in animals with a survival period of from eleven to seventy-seven days; Bast and Blömmendal⁸ observed lesions in rabbits after eight to thirty-one days, which often led to collapse and death, and Crile⁹ noted alterations in rabbits after ninety-six to one hundred and eighteen hours. Piéron¹⁰ and others observed similar changes. In all, the changes were chiefly in the ganglion cells and consisted in disappearance of Nissl granules, displacement of nuclei and vacuolation—in short, alterations of the axonal type, which is known to be reversible. Changes of uncharacteristic nature have been reported in the cells of the liver, the adrenal glands and the thyroid.

Kleitman¹¹ kept subjects awake from forty to one hundred and fifteen hours; Rakestraw and Whittier,¹² forty-eight hours and Krisch,¹³ seventy-two hours. In none were there reported significant changes in the heart rate, blood pressure, temperature, basal metabolic rate or composition of the blood, including the dextrose, nonprotein nitrogen, urea, uric acid, creatinine, chloride and phosphate contents and the alkali reserve. After the subjects had been kept awake for ninety-two to one hundred and forty-three hours, Patrick and Gilbert¹⁴ observed hypothermia, which was also noted by Tarrozzì¹⁵ after nine, thirteen and seven days. Scattered reports of diminution in heart rate, fall of blood pressure, increase of carbon dioxide tension of alveolar air and

7. Okazaki, S.: An Experimental Study of the Lack of Sleep, *Psychol. Abstr.* **2**:628, 1928.

8. Bast, T. H., and Blömmendal, W. B.: Studies in Experimental Exhaustion Due to Lack of Sleep: IV. Effects on the Nerve Cells in the Medulla, *Am. J. Physiol.* **82**:140-146, 1927.

9. Crile, G. W.: Studies in Exhaustion: An Experimental Research, *Arch. Surg.* **2**:196-220 (March) 1921.

10. Piéron, H.: *Le problème physiologique du sommeil*, Paris, Masson & Cie, 1913.

11. Kleitman, N.: Studies on the Physiology of Sleep: I. The Effects of Prolonged Sleeplessness on Man, *Am. J. Physiol.* **66**:67-92, 1923.

12. Rakestraw, N. W., and Whittier, F. O.: The Effect of Loss of Sleep on the Composition of the Blood and Urine, *Proc. Soc. Exper. Biol. & Med.* **21**:5-6, 1923.

13. Krisch, H.: Weiter Beiträge zur Pathophysiologie der "epileptischen motorischen Varianten" und der migranösen Hirnstammsyndrome (Kombination mit Chorea, Schlafsucht), *Ztschr. f. d. ges. Neurol. u. Psychiat.* **98**:80-92, 1925.

14. Patrick, G. T. W., and Gilbert, J. A.: On the Effects of Loss of Sleep, *Psychol. Rev.* **3**:469-483, 1896.

15. Tarrozzì, cited by Kleitman.¹¹

rise of electrical skin resistance and controversies over decrease in the blood calcium may be found, but there appears to be no correlation of changes which would lead to a conception of the response of the body to such stimulation as this state may call forth. This, as will be seen, is in contrast to the conception with regard to exhausting muscular exertion. However, a clue to the trend of future research is found in the recent studies on the hypothalamus, in which the condition of sleep is found to be the antithesis of the activities and reactions of the sympathetic and somatic processes involved in emotional expression. Thus, Ranson¹⁶ stated:

The hypothalamus is the center for integration of sympathetic and somatic reactions involved in emotional expression, and its activation produces a thoroughly excited animal with active visceral and skeletal musculature.

He found that bilateral destruction of the lateral hypothalamic area leads to somnolence, and it is this same area stimulation of which produces most readily combined sympathetic and somatic excitation. This area he concluded to be the center for the integration of emotional expression, and he suggested that it be termed the waking center. When it is thrown out of function, somnolence ensues.

Such fatigue as may be the result of healthy persons' being subjected to exhausting physical exercise has been more adequately studied. Hastings¹⁷ has well described the condition necessary for efficient muscular activity. Such activity is dependent on "an adequate supply of material for combustion, of oxygen to effect this combustion, and upon the removal of the products of cellular activity." Inability to maintain this acceleration of processes and to keep them integrated as a unit comprises the conception of fatigue.

During a bout of severe exercise, lactic acid is formed rapidly; such as cannot be removed by oxidation at the time must accumulate in the muscles. During the period of exercise the amount of oxygen which has been taken in by the subject is small as compared with that needed to prevent the accumulation of lactic acid. The additional greater amount of oxygen known as the oxygen debt can be supplied only during the subsequent period of rest. As soon as the exercise is commenced, and continuing well into the period of recovery, increase in rate and depth of respiration occurs. From whatever stimulus this follows, there is an increase both in carbon dioxide pressure and in the hydrogen ion concentration of the blood. The respiratory quotient is increased.

16. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, *Arch. Neurol. & Psychiat.* **41**:1-23 (Jan.) 1939.

17. Hastings, A. B.: *The Physiology of Fatigue*, Public Health Bulletin 117. United States Treasury Department, Public Health Service, 1921.

Some of this effect is due to the greatly increased rate of ventilation and some to the rapidly accumulating lactic acid, which results in one or another manner in the displacement of carbon dioxide. In spite of the increased ventilation, there remains an accumulation of lactic acid in the body. Therefore, after the conclusion of severe exercise, when the intake of oxygen is reduced, the elimination of carbon dioxide continues until the hydrogen ion concentration of the blood is reduced to its resting level.

The participation of the nervous system in effecting a coordination of some of the processes necessary to meet the emergency of increased muscular activity has been described by Cannon.¹⁸ He has shown how, when continuous muscular activity reduces the sugar in the blood, the sympathetic mechanism of the adrenal is stimulated and sugar is liberated from storage in the liver.

As is well known, vigorous muscular activity is associated with the development of heat. Cannon pointed out that should there be no loss of heat the increase of oxygen intake during vigorous steady exercise would be enough to raise the body temperature to 109 F. To protect the body, the sympathetic nervous system acts to produce peripheral vascular dilatation, to the end that the hot blood loses some heat by convection and conduction and by liberation of sweat, with resulting evaporation and carrying off of heat. A mechanism to prevent dangerous acidosis from increased lactic acid and carbon dioxide lies in relaxation of the bronchioles through stimulation of the sympathetic nerve supply to the bronchioles, with resulting increase in ventilation. To meet the greatly increased need of oxygen, blood is driven from the splanchnic area by splanchnic vasoconstriction, and the heart rate increases and the blood pressure increases. In addition, by contraction of the spleen there may be an increase of red corpuscles in circulation, amounting to as much as 25 per cent.

The important relation of starvation to fatigue may be explained by the fact that carbohydrate is the real fuel used by contracting muscles, and when the carbohydrate store has been used up, as under conditions of deprivation of food, other substances, such as fat, can be called on and the respiratory quotient may be lowered, the blood sugar may be diminished and acetone may appear in the urine.

Of great interest are Hill's¹⁹ experiments on vapor pressure. He demonstrated a considerable rise of osmotic pressure in a frog's muscle stimulated anaerobically and showed an increment in the osmotic pressure

18. Cannon, W.: The Sympathetic Division of the Autonomic System in Relation to Homeostasis, *A. Research Nerv. & Ment. Dis., Proc.* **9**:181-198, 1930.

19. Hill, A. V.: *Adventures in Biophysics*, Philadelphia, University of Pennsylvania Press, 1931, p. 29.

of the blood of a man drawn a few seconds or less after the subject had run at maximum speed while standing in one position. He said:

May not such a change of osmotic pressure, leading temporarily to a large upset in the water distribution of the organism, be the cause of some of the phenomena of fatigue? Might not, for example, an osmotic suction of one atmosphere suddenly applied, considerably upset the nervous system?

The bodily changes associated with emotions are well known—sorrow with its tears; worry and vasoconstriction; joy and vasodilatation; even temporary loss of muscular control or extraordinary muscular power, inhibition of salivary and gastric secretion and contraction of the stomach and intestines. Cannon²⁰ has shown that strong emotions, such as fear and rage, evoke the same associated changes as those brought about by vigorous muscular movement—liberation of sugar from the liver, pouring out of sweat, dilatation of the bronchioles, constriction of the splanchnic area, acceleration of the heart and discharge of corpuscles from the spleen into the circulatory system—responses rendering the organism more capable of supreme and prolonged struggle.

It has been seen that exhaustion accompanying extreme muscular activity, loss of sleep or hunger and thirst alone constituted a condition from which recovery was quickly effected by sleep, and that in itself the exhaustion was unassociated with the evidence of neurosis. Likewise, fear and horror were experienced, and during the time that circumstances warranted their occurrence neurosis was rarely encountered. Dide,²¹ chief medical officer to the twenty-fourth battalion of *chasseurs alpins*, said:

Two companies who were collected to support the attack, if required, were kept standing still and were subjected to accurate fire by heavy artillery. The losses were high, inasmuch as we had to remove 32 bodies which had been almost blown to pieces, as well as the wounded. After two hours of this experience some movement took place. It was thought that the order had been given to retire, and I saw half a company making their way to my aid post in a bewildered condition, just as if they had been surprised in their sleep. I gave them a few words of encouragement, and, new orders having meanwhile arrived, they returned to the firing line in the most perfect order.

This episode seemed to Dide to combine all the circumstances likely to cause nervous disturbances: the extreme violence of the bombardment (several explosions a second), the heavy losses in men killed, the appalling spectacle of the mutilated bodies and the absence of anything to distract attention, the attack occurring as it did to troops standing still

20. Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, ed. 2, New York, D. Appleton and Company, 1929.

21. Dide, M., in discussion on Vincent, C.: *Sur les accidents nerveux déterminés par la déflagration de fortes charges d'explosifs*, *Rev. neurol.* **23**:573-609, 1916.

and waiting to fight. Nevertheless, he observed not a single case of nervous disturbance.

du Roselle and Oberthur²² said:

These men, with their haggard and hallucinated look, who make no reply to questions and do not recognize their officers or fellow-men, retain a lively instinct of self-preservation in their subconscious mind.

Vincent.²³ likewise, made the observation:

In places where projectiles came in large numbers causing deaths and wounds I never saw any hysterical phenomena, such as fits, contractures, or paralysis of one or more limbs. I saw emotional phenomena only, of which the most frequent were tears, trembling, a state of hebetude in which the man does not move or answer questions, tachycardia, tachypnoea and micturition.

Babinski and Froment²⁴ cited still another incident.

The last circumstance deserves to be related in some detail, for it may have seemed *a priori* specially suitable for the development of hysterical symptoms. It was on August 28, 1914, when the ambulances 1/14 and 3/14 had just been drawn up side by side by the Burgonee after a period of ten days' continuous retirement which had had a powerful demoralising effect upon the men. All of a sudden, heavy shells, which had hitherto been falling at about a mile off, began to fall nearer and ended by reaching the ambulance. Although the bombardment lasted only an hour, out of an effective of forty men one of the ambulances had seven wounded and twelve killed. The latter were hardly recognizable, in many of them the trunk had been separated from the limbs, which had been torn and hurled to a distance. The effects of the bombardment had made a great impression upon the orderlies, to whom this painful episode was unexpected, and constituted their baptism of fire. And yet, neither that day nor during the following weeks did any of them present any hysterical manifestations.

Some mention should be made of noise. Aside from impairment of hearing, sudden loud noise followed by a startle is, as pointed out by Kennedy,²⁵ associated with an increase of cerebrospinal pressure. There are increased blood pressure, increased heart beat and decreased gastric motility. Although noise has been studied chiefly in relation to efficiency in industry and has been found to produce fatigue or varying degrees of exhaustion, further research is indicated, if only from the report of Morgan and Morgan²⁶ on an abnormal pattern of behavior in rats.

22. du Roselle and Oberthur: Notes additionnelles (Vincent, C.: Sur les accidents nerveux déterminés par la déflagration de fortes charges d'explosifs), Rev. neurol. **23**:598-603, 1916; cited by Babinski and Froment.²⁴

23. Vincent, C., cited by Babinski and Froment.²⁴

24. Babinski, J., and Froment, J.: Hysteria of Pithiatism and Reflex Nervous Disorders in the Neurology of War, London, University of London Press, 1918.

25. Kennedy,⁸ p. 1931.

26. Morgan, C. T., and Morgan, J. D.: Auditory Induction of Abnormal Pattern of Behavior in Rats, J. Comp. Psychol. **27**:505-508, 1939.

Although the response was originally produced by the presentation of a situation which heavily taxed the animal's capacities for discrimination (Pavlov²⁷) or by a simultaneous blast of air with the presentation of a problem of insoluble nature (Maier²⁸), Morgan and Morgan were able to produce similar reactions by the presentation only of the noise of the air blast, which was removed several feet from the animal. There ensued circling movements, ticlike movements and then the assumption of tonic immobility resembling catatonic stupor, in which visual, auditory and tactile stimuli evoked no response.

Extremes of fatigue, and likewise the responses associated with hunger, thirst and noise, have been shown to be relatively quickly cured by sleep without any observable relation to the development of the neurosis. Fear and other extremes of emotional disturbances experienced during the action evoking them have been shown, rather, to militate against the appearance of hysteria. To all, however, my associates and I have observed severe bodily responses, many of them of a similar nature, calling forth the reserves of the body by participation of the peripheral and central representation of the sympathetic nervous system. What relation this bears to the later development of the neuroses I believe deserves present serious attention.

BLAST CONCUSSION

On many occasions, as the result of the blast of an exploding shell, soldiers have been thrown violently against a parapet, to the ground, buried, bruised and physically injured. Often injury to the central nervous system resulted, at times serious, but usually with rapid recovery. With these injuries I am not at the moment concerned. There is a group of cases, however, in which changes occur as the result of rapid and extreme changes in atmospheric pressure and without the production of external evidence of injury, but with ensuing severe disorders. Illustrative of this is Bartlett's²⁹ description of "a valley of death" in the Dardanelles.

In one corner seven Turks, with their rifles across their knees, are sitting together. One man has his arm around the neck of his friend and a smile on his face as if they had been cracking a joke when death overwhelmed them. All now have the appearance of being merely asleep; for of the seven, I only see one who has any outward injury.

Such examples were not uncommon during the first World War and in subsequent wars. In addition, many internal injuries may result

27. Pavlov, I. P.: *Conditioned Reflexes*, London, Oxford University Press, 1927.

28. Maier, N. R. F.: *Studies of Abnormal Behavior in the Rat: IV. Abortive Behavior*, *J. Exper. Psychol.* **27**:369-393, 1940.

29. Bartlett, A., cited by Mott.⁴⁶

from the blast of an exploding shell, hemorrhage of the lungs, rupture and hemorrhage of the viscera or hemorrhage and other injury to the central nervous system—all without significant external injury.

To understand the effects of high explosive bombs, it is useful to know something of the nature of high explosives. In handbook 5^{29a} "Air Raid Precautions," series may be found a concise description: An explosive is a substance which, on application of a suitable stimulus to a small portion of the mass, is converted in a very short time into other, more stable substances, largely or entirely gaseous.

A low explosive burns by a process of rapid combustion, but a high explosive functions in a far more rapid manner, known as detonation. The conversion of the explosive into a more stable gas proceeds by a wave of detonation, which passes through the substance with a velocity of detonation varying from 15,000 to 25,000 feet (4.5 to 7.6 kilometers) a second, according to the explosive used. The time taken for the detonation of the main filling of a 500 pound (227 Kg.) bomb may be assumed to be of the order of one ten-thousandth second.

The explosive is thus, within its own volume, suddenly converted into gas at a very high temperature and pressure. The effect is a sudden blow on the immediate surroundings, the violence of which depends on the velocity of detonation and the pressure produced. The high pressure generated by the conversion of the solid explosive into gas causes the metal case to swell until it reaches about one and a half times its original diameter, when it bursts into fragments or splinters. Immediately fragmentation occurs, the hot compressed gases are suddenly released and force their way past the fragments with a velocity of the order of 7,000 feet (2 kilometers) per second. The air in contact with the gas is suddenly compressed, with the result that an intense blast pressure pulse, or shock wave, is formed at the boundary of the gases. This air-borne shock wave is analogous to an ordinary sound wave, except that its amplitude and velocity, and I might add its wave form, are greater. As the wave travels outward from the source, its amplitude and velocity concurrently decrease, the velocity becoming stable at about 1,100 feet (335 meters) per second. The violently expanding gases may be regarded as constituting a localized zone of expansion. In this zone there is essentially an outward movement of gas, giving rise both to intense pressure and to dynamic forces, which rapidly diminish with distance from the center of the explosion. On the other hand, the blast, i. e., the pressure created by explosion in the air which surrounds the explosion itself, is propagated by wave motion through the air without bodily movement of the air and persists for considerable distances. Analogous waves are also generated in the earth or other target in or

29a. Air Raid Precautions, Handbook 5, London, His Majesty's Stationery Office, 1939.

on which the bomb explodes. The probable maximum distance of the outward movement of gases and air is 25 feet (7.6 meters) when the bomb bursts in the open air.

The shock wave consists of an initial positive pressure phase followed by a negative phase, which is probably followed by a small, decaying oscillation. In the initial positive phase the pressure rises almost instantaneously to a maximum and then decreases linearly to zero, and the suction phase follows. The total duration of the combined positive and negative phases is about one-thirtieth second, whether the distance is 50 or 200 feet (15 or 60 meters) from the bomb, but the duration of the negative phase varies from three to six times that of the positive phase. For a 70 pound (32 Kg.) charge, Zuckerman³⁰ said that the positive phase lasts six-thousandths second and the negative phase three-hundredths second. In the case of a 60 pound (27 Kg.) charge, the velocity is almost 1,500 feet (457 meters) per second at 30 feet (9 meters) from the charge. The wave pressure is highest in the region of the explosion and falls off rapidly the farther it moves away. Thus, 15 feet (4.5 meters) from a 125 pound (56.7 Kg.) charge the hydrostatic pressure may be of the order of 220 pounds (99.8 Kg.) per square inch (6.5 sq. cm.), whereas 50 feet (15 meters) away the maximum pressure recorded will not be more than 10 pounds (4.5 Kg.), these figures representing pressure in excess of normal atmospheric pressure of 15 pounds (6.8 Kg.) per square inch. Close to the explosion the wind pressure may be as great as the hydrostatic pressure. It falls more rapidly with distance than does hydrostatic pressure. Of importance is the author's observation that the velocity and duration of a pressure wave are such that a body as large as a human being could certainly be completely immersed for an instant in a wave of almost uniformly raised pressure. The wavelength of the negative phase is given by the "Handbook" as 30 feet (9 meters).

Sutherland³¹ stated that in some cases of blast compression, wave pressures up to 200 atmospheres have been observed. When a wave meets a wall, the wall may be set into vibrations like a diaphragm, and the impact may be violent enough to fracture the skull of any one resting against the wall. This, of course, is in case the wall is in an enclosed space.

Much has been written about the "suction" effect, variously described as recoil, aspiration or decompression. One explanation is that the hot gases expand to a volume determined by their high temperature and then cool and contract to a smaller volume, with creation of a partial vacuum. It is probable, however, that no overshooting results.

30. Zuckerman, S.: Experimental Study of Blast Injuries to the Lungs, *Lancet* 2:219-224, 1940.

31. Sutherland, G. A.: The Physics of Blast, *Lancet* 2:641-642, 1940.

It seems more likely that the effect is the result of a wave of rarefaction following immediately on the wave of compression. The order of change of pressure to less than atmospheric is, of course, far less than the positive change and could never exceed 15 pounds per square inch; as already noted, its duration is far greater.

In addition to the effects of change in atmospheric pressure and the dynamic effect of a traveling wave, an explosion in a confined space instantly deoxygenates the air and produces a high concentration of carbon monoxide and nitrogen monoxide, which Hill³² stated, if inspired by man, may produce death. Likewise, Sydenham³³ expressed the opinion that the detonation of 50 to 100 pounds (22.7 to 45.4 Kg.) of trinitrotoluene could produce enough carbon monoxide in the immediate vicinity to give rise to the characteristic poisonous effect of this product. Logan³⁴ also noted that under favorable conditions of undue heavy atmospheric conditions, violent and prolonged bombardment may cause a collection of carbon monoxide of sufficiently high concentration to cause poisoning; he noted the presence of carbon monoxide in the blood of men who had been killed or wounded and observed that the substance might also be found when the bursting shell had not produced any external wound.

From the foregoing observation, it may be seen that the effect on any object or man will depend, among other things, on the distance from the center of explosion. Thus, Carver and Dinsley³⁵ described three zones about the point of detonation: In the nearest, or the zone of brizance, all life is destroyed. Hughes and Banks³⁶ noted the rending of soldiers into pieces, disintegration rather than rending, and stated that these effects were less often noted in the open and were not much felt beyond 30 yards (2.7 meters). In the next zone, carbon monoxide was under compression, and death without external evidence of injury occurred, with capillary hemorrhages in the nervous system; farther out in this zone a state of stupor and awkward gait were noted. In zone 3, no serious lesions were produced, but later neuroses developed. These zones must differ in size, dependent on the size and character of the explosive, and such a division is valuable only to point out the varying degrees of effect, from that of the greatest disruptive force to that in which demonstrable changes are absent.

32. Hill, L., cited by Mott.⁴⁶

33. Sydenham, T., cited by Mott.⁴⁶

34. Logan, D. D.; Detonation of High Explosive in Shell and Bomb, and Its Effects, *Brit. M. J.* **2**:864-866, 1939.

35. Carver, A., and Dinsley, A.: Some Biological Effects Due to High Explosives, *Brain* **42**:113-129, 1919.

36. Hughes, B., and Banks, H. S.: War Surgery from Firing-line to Base, London, Baillière, Tindall & Cox, 1918.

It may be of interest to inquire into the mechanism whereby the body is affected by such environmental change.

With respect to injury to the body in general, and to the lungs in particular, there has been some difference of opinion, but recently evidence is being adduced that, for the most part, it is brought about by the blow of the expanding, rapidly moving shell of increased pressure. As to the effect on the lungs, the belief has been expressed by some that the lesions are the result of lowering of alveolar pressure by the suction wave, acting through the respiratory passages with consequent rupture of the alveolar capillaries. This possibility was suggested by Logan and by Shirlaw³⁷ and was indicated in the French shelter tests, and it was also the view held in discussions on the casualties which occurred in Spain. The second possibility is that the lesions in the lungs are due to the impact of the pressure wave on the chest wall. Kretzschmar,³⁸ likewise, subscribed to this belief, and the experiments of Zuckerman strongly suggest that this is the mechanism responsible for injury to the lung.

With respect to injury to the nervous system, it has been suggested that as the result of reduced atmospheric pressure, during the suction part of the wave, gas emboli are formed, as in caisson disease. Of this explanation, Hill³² said that he could not see how alteration of air pressure could do more than act on the gas in the intestine and in the lungs, and he expressed the belief that such injuries as occurred were the result of deoxygenation of the blood or of concussion. Surgeon General Stevenson³⁹ suggested that the sudden increase of atmospheric pressure, lasting only a fraction of a second, could not produce death, as in cases of caisson disease (the latter, of course, is concerned more with the decrease of pressure, but the time relations hold true), and he likewise concluded that the results were due to concussion. But Thomas⁴⁰ pointed to the sudden snatching away of atmospheric pressure around the bodies by the voracious vacuum suddenly produced outside. Many of the French writers, including Ravaut,⁴¹ Heitz,⁴² Guillaïn⁴³ and Sollier

37. Shirlaw, G. B.: *Casualty: The Training, Organization and Administration of Civil Defence Casualty Services*, London, Secker & Warburg, 1940.

38. Kretzschmar, C. H.: *Wounds of the Chest Treated by Artificial Pneumothorax*, *Lancet* **1**:332-334, 1940.

39. Stevenson, W. F.: *Note on the Cause of Death Due to High-Explosive Shells in Unwounded Men*, *Brit. M. J.* **2**:450, 1915.

40. Thomas, J. L.: *Death from High Explosives Without Wounds*, *Brit. M. J.* **1**:599, 1917.

41. Ravaut, P.: *Etude sur quelques manifestations nerveuses, déterminées par le "vent de l'explosif,"* *Bull. Acad. de méd., Paris* **37**:717-720, 1915.

42. Heitz, J.: *Cinq cas de paraplégie organique consécutive à des éclatements d'obus sans plaie extérieure*, *Paris méd.* **17**:78-85, 1915.

43. Guillaïn, G.: *Centre neurologique de la sixième armée*, *Rev. neurol.* **23**:733-736, 1916.

and Chartier,⁴⁴ ascribed the changes in the central nervous system to the atmospheric decompression resulting from the explosion; thus, Guillaïn said that the nervous phenomena resulting from the detonation of modern projectiles are analogous to those of caisson disease and result from the rapid changes in atmospheric pressure.

With regard to subjection of man to increase of pressure alone, it is well known that enormous pressures may be exerted on biologic tissue without apparently disturbing its function. In relation to caisson disease, Haldane pointed out that when the body, which, with the exception of bone and air-containing organs, is similar to a fluid mass, was surrounded by an increase of pressure, every particle instantly attained the same degree of pressure as that to which the body was subjected. In this connection, I may mention some recent unfinished experiments which Dr. Finkelman, Dr. Tigay and I have been conducting. On measuring the cerebrospinal fluid pressure of dogs subjected to increase of atmospheric pressure in a pressure chamber by means of a balancing manometer outside the chamber, we found that at the height of compression the cerebrospinal fluid pressure was less, and at the return to normal pressure it was higher, than the pressure of the ambient air. This seeming disagreement with Haldane's⁴⁵ statement we believe to be due to the fact that atmosphere can act on the intracranial contents only through the entering and emerging viscous elastic blood vessels at the base of the skull.

In regard to the possible formation of gas bubbles, although the order of change of pressure from the height of compression to the lowest point of decompression would be sufficient, the time is too short to permit the escape of gas from the blood. With regard to the effect of some physical blow, such as concussion, on the nervous system, it was generally stated that the cerebrospinal axis was in some way shaken up. Logan mentioned the possibility that *commotio cerebri* would be caused by the transmission of intense vibrations through the bony structures to the central nervous system. However, it is known that a detonation does not produce a succession of waves, as in vibration, but a single one. Nevertheless, the body might be made to vibrate according to its own frequency, but the amplitude would be small indeed.

Mott⁴⁶ expressed the opinion that high pressures might suspend vital centers in the medulla, but Hooker⁴⁷ showed from his experiments

44. Sollier, P., and Chartier, M.: *La commotion par explosifs et ses conséquences sur le système nerveux*, Paris méd. **17**:406-414, 1915.

45. Haldane, J. S.: *Respiration*, New Haven, Conn., Yale University Press, 1935, p. 331.

46. Mott, F. W.: *The Lettsomian Lectures on the Effects of High Explosives upon the Central Nervous System*, *Lancet* **1**:331-338, 441-449 and 545-553, 1916.

47. Hooker, D. R.: *Physiological Effects of Air Concussion*, *Am. J. Physiol.* **67**:219-274, 1924.

that such was not the case. Mott stated the belief that the action of compressed gas and air in striking the body as a solid would produce vascular disturbances.

In addition to the effect of direct concussion by burial or bruising through impact against the ground or a wall or parapet, much remains to be explained about indirect concussion by impact of the moving wave of compression. Although Hooker raised the question whether the symptoms of air concussion were not ultimately similar to those of traumatic concussion, the answer is not at hand. In relation to this, since in cases of blast concussion clearcut histologic evidence of injury is absent, and since the same observation holds true for concussion experimentally produced in animals by blows delivered at a velocity of from 25 to 28 feet (7.6 to 8.5 meters) per second, Fulton ⁴⁸ asked whether there is anything in common between direct traumatic concussion and blast concussion. He stated:

A wave of moving pressure that gives acceleration to the body by virtue of its impact on the body wall—and hence imparts an acceleration to the body as a whole, including the head—reproduces in a very precise manner the type of acceleration or deceleration known to be essential for the traumatic-concussion syndrome.

Other causes for the circulatory collapse described by Hooker should be sought, and it is of interest to recall the experiments of Capps and Lewis ⁴⁹ on the condition which they called pleural shock. It would also be of interest to measure the order of changes in intracranial, venous, arterial and cerebrospinal fluid pressure which follow sudden, severe compression of the chest and abdomen. There remains also the question of fat embolism. McKibben ⁵⁰ said that observations on dogs indicate that there are no quantitative differences between the fat, recognized histologically, in the vessels of normal control animals, and that demonstrated in dogs subjected to concussion and prolonged anesthesia. However, de Gutiérrez-Mahoney ⁵¹ reported that in cases of concussion widespread demyelination of nerve tracts, followed by the transient appearance of fat droplets throughout the cerebral substance, can be detected; outspoken fat embolism may also result.

48. Fulton, J. F.: Blast and Concussion in Present War, *New England J. Med.* **226**:1-8, 1942.

49. Capps, J. A., and Lewis, D. D.: Some Observations on Pleural Reflexes, *Surg., Gynec. & Obst.* **7**:243-246, 1908.

50. McKibben, P. S.: A Note on Intravascular Fat in Relation to the Experimental Study of Fat Embolism in "Shell Shock," *Am. J. Physiol.* **48**:331-339, 1919.

51. de Gutiérrez-Mahoney, W.: Pathogenesis of Traumatic Unconsciousness, *War Med.* **1**:816-823 (Dec.) 1941.

The fat droplets and fat emboli tend to disappear within three or four hours, which explains the failure to note them in tissues of animals killed and fixed after longer periods.

As to the effect of the forces of blast on the body, in 1915 Sencert⁵² described the case of a man who was able to tell how, as he was going forward, a large caliber shell fell less than a meter in front of him and exploded. He fell back and lost consciousness, was picked up and, when after ten hours, he was brought to the ambulance, was found to have no wound other than small cutaneous wounds of the right arm and one of the fingers of the right hand and the right ear. He died during the night, and autopsy revealed, among other things, a large tear at the base of the middle lobe of the right lung and a pleural tear over the left lung, with herniation of a black lung.

Numbers of men were picked up dead in the vicinity of an explosion without external injury. Isolated reports of the presence of injury to the lungs may be found. Mairet and Durante,⁵³ Rusca⁵⁴ of Berne and Crile⁵⁵ described such injuries in animals exposed experimentally to nearby explosions. It was not, however, until the present war that there was general recognition of the prevalence of injury to the lungs in association with blast. As pointed out by Fulton, Hooker's experimental studies, published in 1924 but arousing little comment, afford the most thorough experimental analysis as yet available. In his experiments, likewise, hemorrhagic lesions of the lung were described. The more recent experiments of Zuckerman graphically showed the vulnerability of the lungs to blast. Although deaths from uncomplicated primary blast are rare in civilian areas, many well authenticated cases have been reported. What was a mystery from 1914 to 1918 has become a commonplace.

To introduce the subject of injuries to the nervous system, an early case of Mott's⁵⁶ may be cited. A soldier became rather nervous at the Somme and later underwent intense bombardment for some four hours. Although he said he "could not stand it much longer," he carried on for twelve hours more, when perhaps six shells went over. One of the shells burst about 10 feet (3 meters) away, just behind the dugout. The

52. Sencert, L.: Rupture des deux poumons par le "vent du boulet," Bull. et mém. Soc. de chir. de Paris **41**:79-82, 1915.

53. Mairet, A., and Durante, G.: Contribution à l'étude expérimentale du syndrome commotionnel, Montpellier méd. **39**:902-915, 1917.

54. Rusca, F.: Experimentelle Untersuchungen über die traumatische Druckwirkung der Explosionen, Deutsche Ztschr. f. Chir. **132**:315-374, 1915.

55. Crile, G. W.: Research into the Effects of Air Concussion on Animals, with Especial Reference to the Observed Effects of Air Concussion on Soldier, unpublished data, 1917.

56. Mott, F. W., cited by Southard, E. E.: Shell-Shock and Other Neuro-psychiatric Problems, Boston, W. M. Leonard, 1919.

first day of the bombardment he was tremulous and depressed, and later was coarsely tremulous in the limbs. On February 23, after the bombardment, he cried and was unable to walk or do any sort of work. He did not answer questions. The pupils were dilated. On the evening of February 23 he was admitted to the field hospital in acute mania, shouting "keep them back; keep them back." Thus far the description could in a general way fit hundreds of cases, but on the morning of February 24 he awakened apparently well and then suddenly died. With the exception of some small scratches on the anterior wall of the chest, there were no signs of external violence. Both lungs were edematous, and the lower lobe of the left lung showed considerable hemorrhage. Hemorrhages were observed throughout the brain in the corpus callosum, the internal capsule, the pons and the bulb. In addition, generalized chromatolysis of nerve cells, comparable to that described by Crile in cases of exhausted and wounded soldiers, was observed.

That injury to the central nervous system can occur without the evidence of external wounds has been amply reflected by the literature of the first World War. A few instances may be mentioned: cases of paraplegia, Heitz,⁴² Babinski,⁵⁷ Roussy and Lhermitte,⁵⁸ Ravaut,⁵⁹ Froment,⁶⁰ Guillain and Barré⁶¹ and Hurst⁶²; cases of hemiplegia, Marie and Lévy,⁶³ Guillain,⁶⁴ Harzbecker⁶⁵ and Souques, Mégevand and Donnet⁶⁶ cases of hemorrhage in the cerebrum and medulla, Leriche,⁶⁷

57. Babinski, J., cited by Southard, E. E.: *Shell-Shock and Other Neuropsychiatric Problems*, Boston, W. M. Leonard, 1919.

58. Roussy, G., and Lhermitte, J.: *Blessures de la moelle et de la queue de cheval*, Paris, Masson & Cie, 1918, p. 102.

59. Ravaut, P.: *Les hémorragies internes produites par le choc vibratoire de l'explosif*, *Presse méd.* **23**:114, 1915.

60. Froment, J.: *Paraplégie par déflagration d'obus*, *Rev. neurol.* **22**:1205-1214, 1915.

61. Guillain, G., and Barré, J. A.: *Les troubles sphinctériens transitoires dans les commotions par éclatement de gros projectiles sans plaie extérieure*, *Bull. et mém. Soc. méd. d. hôp. de Paris* **41**:1114-1118, 1917.

62. Hurst,⁴ p. 120.

63. Marie, P., and Lévy, G.: *Un cas d'hémiplégie organique par commotion sans blessure*, *Rev. neurol.* **24**:44-45, 1917.

64. Guillain, G.: *Hémiplégie organique consécutive à un éclatement d'obus sans plaie extérieure*, *Presse méd.* **23**:429, 1915.

65. Harzbecker, O.: *Ueber die Aetiologie der Granat-Kontusionsverletzungen*, *Deutsche med. Wchnschr.* **40**:1985, 1914.

66. Souques, A.; Mégevand, J., and Donnet, V.: *Importance de l'analyse précoce du liquide céphalo-rachidien pour le diagnostic des syndromes cérébro-médullaires dus au "vent de l'explosif"*, *Bull. et mém. Soc. méd. d. hôp. de Paris* **39**:917-926, 1915.

67. Leriche, R.: *Des lésions cérébrales et médullaires produites par l'explosion à faible distance des obus de gros calibre*, *Lyon chir.* **12**:343-350, 1914-1915.

and in the optic thalamus. Léri and Schäffer⁶⁸; many cases of meningeal hemorrhage, Guillain and Barré,⁶⁹ Leriche⁶⁷ and Sukhanoff,⁷⁰ and cases of disturbances of pupillary and sphincteric reflexes.

What relation the existence of such lesions bears to concepts concerning the neuroses is a matter for conjecture. The important thing is that such lesions do occur. To how many have been overlooked I shall allude further on. What occurs in the outermost, yet noxious, zone of detonation?

Until further research may be done and until careful examinations may be made on the field soon after the supposed injury, this question will remain unanswered. It is interesting to review the observations of Aschaffenburg⁷¹ on 74 soldiers examined in Flanders. Of these, 67 showed unmistakable signs of localized organic lesions of the central nervous system, although not as a rule of serious nature. A second examination a week later showed that some, though not all, of the phenomena had disappeared. The minor changes, such as increase of cerebrospinal fluid pressure, increase of protein, xanthochromia and hemorrhage into the spinal fluid, so frequently reported when examinations were performed soon after injury, suggest that at times when no such changes were reported it was because they were not sought for.

In some instances in which a soldier, having been exposed to the blast of a nearby exploding shell, died a short time later, histologic examination of the nervous system was made. Of cases in which the man survived but later may have died of some other cause, no reports have become available.

In the first group, there have been reported congestion of the brain, minute, punctate hemorrhages on the surface of the brain, considerable ecchymosis on each side of the great sinuses, subpial hemorrhages, hemorrhages into the vascular sheaths in the corpus callosum, internal capsule, pons and bulb, and generalized chromatolysis of cells, including the vagoaccessory nuclei (Mott⁷²). In Mott's cases, the changes were similar in many respects to those he had observed with carbon monoxide poisoning. Likewise, there have been reported extravasation of blood

68. Léri, A., and Schäffer, H.: Hématobulbie par commotion; survie, syndrome bulbaire complexe, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:845-848, 1916.

69. Guillain, G., and Barré, J. A.: Hémorragie méningée consécutive à une commotion par éclatement d'obus sans plaie extérieure. Méningite à pneumocoques mortelle secondaire, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:898-900, 1917.

70. Sukhanoff, S. A.: Influence of Wind Contusion on the Central Nervous System, Russk. vrach. **14**:1010-1013, 1915.

71. Aschaffenburg, cited by Mott.⁷²

72. Mott, F. W.: The Microscopic Examination of the Brains of Two Men Dead of Commotio Cerebri (Shell Shock) Without Visible External Injury, J. Roy. Army M. Corps **29**:662-678, 1917.

into the substance of the lower surface of the orbital lobe, subdural hemorrhage, punctate hemorrhage of the brain (Chavigny⁷³), localized meningeal hemorrhage (Roussy and Boisseau),⁷⁴ softening of the anterior horn cells and the posterior columns of the spinal cord, ependymal gliosis and ischemic necrosis (Claude and Lhermitte⁷⁵). In the second group, the lesser signs demonstrable during life, such as increase of cerebrospinal fluid pressure, bloody spinal fluid and increase of cells and protein in the fluid, have been mentioned.

Of considerable importance in relation to the infrequency of signs of organic lesions in the central nervous system are the reports on the effect produced in animals subjected to experimental detonation of high explosives. In some of the earlier experiments, such as Crile's,⁵⁵ there was rupture of the minute blood capillaries in the alveoli of the lungs (and in 5 men as well), and in 1 a hemorrhage in the dura occurred, but no gross hemorrhages were noted in the brain and spinal cord. Mairet and Durante⁵³ reported minute scattered hemorrhages throughout the central nervous system, particularly about the spinal nerve roots.

Rusca⁵⁴ of Berne noted direct and contrecoup lesions in the brain, and Marinesco saw some hemorrhages in the nervous system; Carver and Dinsley's³⁵ report was similar to that of Mairet and Durante,⁵³ but Hooker⁴⁷ was unable to discover any evidence of injury to the brain. In 1 instance he noted a confluence of petechial hemorrhages in the dura. In Zuckerman's⁷⁶ material, studied by Greenfield and Clark which consisted of monkeys exposed to high pressure, 110 pounds (49.9 Kg.) per square inch, extradural hemorrhages were observed in the roots of the thoracic nerves. In 2 animals which died, hemorrhage occurred at the central ends of the posterior column and in the dorsal commissure. A greater number of animals had edema about the central canal. No changes were observed in the cortex, midbrain, pons or medulla. In rabbits the changes were more prominent. Pial hemorrhages occurred on the surface of the cortex, but not in either the gray or the white matter of the brain.

In the case of the pheasant which had been exposed to blast, reported by Stewart, Russel and Cone,⁷⁷ congested capillaries of the forebrain,

73. Chavigny, D.: Les explosions du champ de bataille; leur rôle et leur mécanisme pathogènes, *Ann. d'hyg.* **26**:5-25, 1916.

74. Roussy, G., and Boisseau, J., in discussion on Vincent, C.: Sur les accidents nerveux déterminés par la déflagration de fortes charges d'explosifs, *Rev. neurol.* **23**:577-585, 1916.

75. Claude, H., and Lhermitte, J.: Troubles médullaires dans les commotions directes mais à distance de la colonne vertébrale, *Paris méd.* **23**:11-14, 1917.

76. Zuckerman, S.: Discussion on the Problem of Blast Injuries, *Proc. Roy. Soc. Med.* **34**:171-188, 1940-1941.

77. Stewart, O. W.; Russel, C. K., and Cone, W. V.: Injury to the Central Nervous System by Blast, *Lancet* **1**:172-174, 1941.

associated with numerous petechial hemorrhages, most numerous in the hypothalamic area, were observed. It is seen that with some exceptions no gross lesions were produced.

Both Zuckerman and Hooker pointed out that symptoms referable to the nervous system may be pronounced and yet little recognizable histologic change be seen. One may allude here to the electromagnetic-shielding property of permalloy, which property is lost when the metal is struck by a blow, and yet no demonstrable change in structure is found.

Extremes of opinion were expressed as to the relation of blast concussion and the neuroses. Roussy and Boisseau⁷⁴ stated the belief that it is exceptional for explosions a long way off to produce organic lesions, and Guillain⁷⁵ asserted that organic lesions following such explosions are frequent. The former stated that the nervous troubles which result should, in the majority of cases, be classified with the so-called hysterical disorders, an opinion concurred in by most British and American writers, and the latter, Guillain, asserted that "many patients are wrongly considered as pithiatic, hysterical, exaggerators or simulators." Between these extremes is the opinion stated by Claude⁷⁹ that whereas most of the patients observed in the Interior are psychoneurotic, it is possible that the functional disorders are kept up by slight structural and physiologic changes.

I have seen numbers of men who, subjected to the blast of nearby exploding shells, had slight signs of organic disturbance. When shortly these manifestations disappeared, signs of a neurosis did not develop. Many investigators have commented on this. Likewise, in many men who had been exposed to changes in pressure a neurosis did not develop later, and the order of the change in pressure seemed to have been the same as that for persons in whom a neurosis did develop. The symptoms of the latter developing neurosis, after the immediate signs of concussion had disappeared, perhaps in some instances while they still persisted, differed in no way from those of the neurosis which appeared when the circumstance of blast was absent or from some of the symptoms which occurred behind the battle front. Nevertheless, the character of the changes produced by blast or their relation to an after-developing neurosis are not known.

To me, one of the remarkable observations is the fact that after exposure to the environmental changes originating in war, wherever

78. Guillain, G., in discussion on Vincent, C.: Sur les accidents nerveux déterminés par la déflagration de fortes charges d'explosifs, *Rev. neurol.* **23**:575-576, 1916.

79. Claude, H., in discussion on Vincent, C.: Sur les accidents nerveux déterminés par la déflagration de fortes charges d'explosifs, *Rev. neurol.* **23**:587-590, 1916.

they occurred—Russia, Germany, France or far-flung countries—the manifestations of neurosis were strikingly the same: confusion, obtusion, delirium, mutism, blindness, paralyses, contractures and analgesia. It appears that certain patterns of behavior are peculiar to certain species; for example, the senseless wing beating of birds when captured, the immobility of fish when touched, the similar reaction of the opossum to fear and the behavior of rats to sound. Does it not seem that the relation of these patterns of behavior to external stimuli in man deserves energetic study?

PHYSIOPATHIC DISTURBANCES

One of the most formidable changes in environment in war is the presence of solid objects moving in the ambient air at high velocity. Inadvertent collision with one of these may result in death or wound. When the wound can be explained by the path taken by the missile no mystery exists. But another group of disturbances was observed in the first World War and gave rise to the old controversy of psychic and somatic.

Here, as expressed by Meige,⁸⁰ one deals with a series of disturbances in which the main symptom is at one time a certain rigidity, at another time a paresis, and sometimes an association of rigidity and paresis which is neither true paralysis nor true contracture, but which results in almost complete immobilization. The circumstances under which these conditions made their appearance, the thermal, trophic and vascular symptoms which accompanied them and the stubbornness with which they resisted all treatment led many investigators to place them in a category of their own.

The condition of paralysis with contracture was designated variously as congealed hand, by Meige; complete paralysis of the hand, by Pitres⁸¹; acromyotonia, by Sicard⁸²; reflex paralysis, by Babinski and Froment,²⁴ and paratonic paresis, by Marie and Foix.⁸³ Babinski and Froment gave a complete description of the condition and stressed the presence of pronounced vasomotor disturbances with segmentary distribution not corresponding to a definite nerve area and predominantly involving the extremities, chiefly the upper. They noted the local hypothermia,

80. Meige, H.; Bénisty, A. (Mme.), and Lévy, G.: Impotence de tous les mouvements de la main et des doigts, avec intégrité des réactions électriques (main figée), *Rev. neurol.* **22**:1273-1276, 1915.

81. Pitres, cited by Bénisty, A. (Mme.): *Treatment and Repair of Nerve Lesions*, London, University of London Press, 1918, p. 131.

82. Sicard, J. A.: L'alcoolisation Tronculaire au cours des acromyotonies rebelles du membre supérieur, *Paris méd.* **6**:509-513, 1916.

83. Marie, P., and Foix: Sur une forme spéciale de "parésie paratonique des muscles moteurs de la main," *Bull. et mém. Soc. méd. d. hôp. de Paris* **40**:127-130, 1916.

with a loss in temperature of from 4 to 5, and at times 8, degrees (C.); the smaller amplitude of the pulse on the affected side, which increased with the application of heat; the atrophy of the tissues of the hand and fingers, with an increase in the size of the joints; the moisture and occasionally the maceration of the skin; the decalcification of the skeleton of the affected part; the mechanical hyperexcitability of the muscles to faradic and galvanic stimuli, with premature fusion of contractions and rarely slight subexcitability, and at times the similar hyperexcitability of the nerve trunks, all of which, likewise, became less on the application of heat. They called attention to the fact that the contractures disappeared only with the deepest chloroform anesthesia and reappeared as anesthesia disappeared, when the tendon reflexes reappeared, and that when the reflexes on the unaffected side were still absent those on the affected side were exaggerated.

That such disorders should be differentiated from the disturbances due to hysteria has been affirmed by many investigators and denied by some. Among those who expressed agreement may be mentioned Sicard⁸² and Guillain and Barré,⁸⁴ who first called attention to their possible organic nature; Meige, Bénisty and Lévy,⁸⁰ who described the vasomotor and thermic disturbances, and Marie and Foix,⁸³ who discussed the hyperexcitability of the affected contracted muscles in cases of injury to nerves. Duvernay,⁸⁵ Gougerot and Charpentier,⁸⁶ Porot,⁸⁷ Souques, Mégevand and others,⁸⁸ Mirallié⁸⁹ and Tinel⁹⁰ placed these disorders in a separate category. Other authors expressed disagreement and concluded that the paralysis and contractures were functional and that the atrophy, circulatory disturbance, cyanosis, hypothermia and mechanical hyperexcitability of muscle and nerve, with slowness of muscular contraction and premature fusion of the faradic contractions, hypotonus and exaggeration of tendon reflexes, all were

84. Guillain, G., and Barré, A.: Les contractures dans la pathologie nerveuse de guerre, *Bull. mém. Soc. méd. d. hôp. de Paris* **40**:67-69, 1916.

85. Duvernay, L.: Des contractures post-traumatiques en chirurgie de guerre, *Paris méd.* **17**:429-436, 1915.

86. Gougerot, H., and Charpentier, A.: Paralysies réflexes et troubles trophiques réflexes consécutifs aux blessures des extrémités, *Ann. méd.* **3**:269-297, 1916.

87. Porot: Manifestations réflexes (motrices, vaso-motrices et trophiques) consécutives à des désarticulations de doigts, *Presse méd.* **24**:439-441, 1916.

88. Souques, A.; Mégevand, J., and others: Troubles de la température locale, à propos d'un cas de paralysie dit réflexe du membre inférieur, *Rev. neurol.* **23**:505-513, 1916.

89. Mirallié, M.: Paralysies réflexes, in *Revue générale de pathologie de guerre*, publiée sous la direction de P. Emile Weil, Paris, Vigot frères, 1916, pp. 19-35.

90. Tinel, J.: Les blessures des nerfs, Paris, Masson & Cie, 1916.

merely disorders due to immobilization or inactivity. Among the latter authors may be mentioned Claude,⁹¹ Camus,⁹² Thomas,⁹³ Roussy and Lhermitte⁹⁴ and Hurst.⁴

Some of the difference of opinion arose out of the observation by certain investigators that the paralysis and contractures were successfully treated by psychotherapy (Roussy, Boisseau and d'Oelsnitz,⁹⁵ Roussy and Lhermitte⁹⁴ and Hurst⁴). All the authors, however, recognized the resistance to psychotherapy and other types of treatment as compared with the responses of other hysterical conditions, and Roussy and Lhermitte stated that the thermal and vasomotor disturbances persist long after motor recovery. Vincent⁹⁷ was convinced at first that the so-called reflex disorders would not resist the treatment so successfully used by him at Tours in cases of hysteria, but he was forced to conclude that, unlike pithiatic phenomena, such disturbances were obstinate.

Theories concerning the pathogenesis of these disorders vary, but many authors have subscribed to the concept of Babinski that it was of the nature of the changes first reported by John Hunter⁹⁸ in relation to weakness and atrophy resulting from lesions of joints. These early observations were confirmed by a number of studies: those of Gosselin,⁹⁹ LeFort,¹⁰⁰ Valtat¹⁰¹ and, lastly, Charcot¹⁰² and Vulpian,¹⁰³ who emphasized the trophic disturbances of the skin, hair and nails, the secretory disorders and coldness of the limb and the cyanosis or dull pink color of the skin and pointed out that, in addition to disease of the joints, all peripheral lesions, including frost bite, burns and more or less deep wounds of the limbs, may become the starting point of such phenomena.

91. Claude, H., in discussion, *Rev. neurol.* **23**:532-536, 1916.

92. Camus, J., in discussion, *Rev. neurol.* **23**:540-542, 1916.

93. Thomas, A., in discussion, *Rev. neurol.* **23**:542-546, 1916.

94. Roussy, G., and Lhermitte, J.: *The Psychoneuroses of War*, London, University of London Press, 1918.

95. Footnote omitted.

96. Roussy, G.; Boisseau, J., and d'Oelsnitz, M.: *Traitement des psychonévroses de guerre*, Paris, Masson & Cie, 1918.

97. Vincent, C.: *Sur le traitement et le pronostic des phénomènes physiopathiques*, *Rev. neurol.* **24**:537-544, 1917.

98. Hunter, J.: *The Works of John Hunter*, London, Longman [and others], 1835, vol. 1, p. 524.

99. Gosselin, cited by Babinski and Froment.²⁴

100. LeFort, cited by Babinski and Froment.²⁴

101. Valtat, E.: *De l'atrophie musculaire consécutive aux maladies des articulations. Etude clinique et expérimentale*, Thesis, Paris, no. 154, 1877.

102. Charcot, J. M.: *Leçons sur les maladies du système nerveux faites à la Salpêtrière*, Paris, A. Delahaye & E. Lecrosnier, 1887, vol. 3, p. 27.

103. Vulpian, A.: *Maladies du système nerveux (moelle épinière)*, Paris, O. Doin, 1886, vol. 2, pp. 541-592.

I recall in recent years the report of Adson and Rowntree¹⁰⁴ on the successful treatment by sympathectomy of the pain, atrophy and vaso-motor and thermal disturbances associated with certain types of arthritis.

In attributing these changes to a reflex disturbance, Vulpian excluded the cases of sympathetic paralysis and described a heterogeneous group of cases of a condition which Graves and Brown-Séquard afterward called reflex paralysis and Weir Mitchell¹⁰⁵ proposed to call paralysis of peripheral origin, or paralysis resulting from peripheral irritation. In this group were included instances of such conditions as hemiplegia and pneumonia and paralysis of an arm after gunshot injury to a thigh. Nevertheless, Weir Mitchell, Morehouse and Keen¹⁰⁶ included some cases which may be compared to those under discussion, such as that of a man bruised in the arm by a shell fragment in whom there later developed tonic spasm of the palmaris longus, brachialis anticus and flexor carpi ulnaris muscles.

Babinski and Froment, although inclining to Charcot's hypothesis of reflex origin, stressed the importance of the sympathetic nervous system in the genesis of these conditions and of the interesting accompaniment of the patient's state of mind. In fact, the mental condition is reminiscent of that of a soldier suffering from causalgia. Meige¹⁰⁷ said of it:

A peculiar state of mind consisting of torpor and inertia, combined with the constant obsession of their infirmity; they keep their eyes on it, and protect it with their other hand, but yet they are in no pain. Solitary, anxious and careworn, making no unnecessary gesture and perpetually on the lookout, they show a perfect motor negativism for the affected limb.

It is fruitless to review the various reasons expressed by authors for the pathogenesis of these disorders, since for the most part they are speculative. It remains, however, for others to study the disturbance from as many approaches as possible. It is of interest to note the report of a number of cases in which particles of metal dust were shown in the muscles by roentgenography; to the presence of these particles Léri and Roger¹⁰⁸ attributed an irritation responsible for the condition

104. Adson, A. W., and Rowntree, L. G.: The Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, *Surg., Gynec. & Obst.* **50**:204-215, 1930.

105. Mitchell, S. W.: Paralysis from Peripheral Irritation, with Reports of Cases, *New York M. J.* **2**:321-355 and 401-423, 1866.

106. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W., Jr.: Reflex Paralysis, the Result of Gunshot Wounds, Founded Chiefly upon Cases Observed in the United States General Hospital, Christian Street, Philadelphia, Circular 6, Surgeon-General's Office, Washington, D. C., Surgeon-General's Office, 1864.

107. Meige, H., in discussion, *Rev. neurol.* **23**:549-552, 1916.

108. Léri, A., and Roger, E.: Sur quelques variétés de contractures post-traumatiques et sur leur traitement, *Paris méd.* **19**:24-52, 1916.

in some cases. Other foreign bodies might, likewise, be present and not demonstrable. In this connection, the recent experiments of Black, Burns and Zuckerman¹⁰⁹ on the wounding mechanism of missiles of high velocity are of great importance. The results suggest that a disproportionate degree of destruction of tissue is caused by bomb splinters of high velocity, owing to the fact that particles lying in their path are thrown radially with sufficient violence to leave a central cavity around which tissues at some distance from the track are momentarily stretched. The same mechanism would hold for other missiles of high velocity.

Among the interesting fields for speculation is the behavior of the muscle, in which connection Babinski and Froment¹¹⁰ theorized that the accumulation of physiologic poisons produced a condition whereby the muscle acted as if it were in the first stages of veratrine poisoning.

With the accession of knowledge concerning the chemical factors involved in muscle contraction, the production of cholinergic substances and the role of esterase, much may be expected from future studies. One field for investigation may be found in the possible sensitization of muscles ordinarily observed after denervation. All will recall how, after removal of the superior cervical sympathetic ganglion, pain and other stimuli giving rise to emotions produce paradoxical dilatation of the pupil. This, as observed in recent unpublished experiments by Davis, Martin and me, may occur as the result of hormonal or chemical stimulation of the ciliary muscles. Lévi and Roger¹⁰⁸ showed that when an Esmarch rubber band is applied to the root of the limb, as far as possible away from the group of muscles which has undergone contracture, circulation in the limb is thus suppressed and after several minutes the contracture disappears. As soon as the elastic band is released, contracture of the parts reappears.

As an illustration of how the cause of a condition may easily be overlooked and lead to speculation, one may cite cases reported under the general heading of paralyzes at a distance. Such were most of the cases reported by Weir Mitchell, Morehouse and Keen, which included instances of a wound of the right side of the neck followed by paralysis of the left arm, flesh wounds of the right thigh and complete paralysis of all extremities, wounds of the right thigh and paralysis of the right arm, wounds of the left thigh and analgesia of the right thigh, wounds of the right thigh and paralysis of the right arm and wounds of the right thigh and weakness and analgesia of the right hand.

109. Black, A. N.; Burns, B. D., and Zuckerman, S.: Experimental Study of Wounding Mechanism of High-Velocity Missiles, *Brit. M. J.* 2:872-874, 1941.

110. Babinski and Froment.²⁴

The cases which I am about to describe were reported by Claude, Vigouroux and Lhermitte¹¹¹ in October 1915 under the name of muscular dystrophy of the myopathic type, a form of paralysis with muscular amyotrophy limited to the trapezius and serratus magnus muscles, sometimes on one side of the body and sometimes symmetric, involving both shoulders.

The remarkable feature in the 4 cases, according to Bénisty,¹¹² was the occurrence of paralyses at a great distance from the wound. The affected muscles were those of the shoulder girdle and the trapezius and serratus magnus muscles. Subsequently, the authors reported another case of paralysis of the trapezius and serratus magnus muscles following a rather superficial wound of the deltoid. Bénisty¹¹² described a case of injury in the scapular region followed by paralysis of the serratus magnus and trapezius muscles. A number of other cases of paralysis of other peripheral nerves such as the sciatic, musculospiral and ulnar, were recorded. The paralyses in these cases were attributed to impairment of nutrition of certain muscles under the influence of traumatism, which gave rise to atrophy and secondarily to paresis.

Every one, remembering the uniform administration of antitetanus serum, has already made the diagnosis, especially in the cases of paralysis of the trapezius and serratus muscles.

In fact, later Lhermitte¹¹³ reported on the effect of antitetanus serum therapy and cited 3 additional cases. He saw some differences between these cases and the cases reported by Claude, Vigouroux and Lhermitte, which, I think, are explained by the fact that in 3 of the latter the bullet wound was in the parotid triangle and the paralysis of the trapezius muscle may well have resulted from this. Kraus and Chaney¹¹⁴ expressed the opinion that the cases were similar and that the significance of injection of antitetanus serum in relation to subsequent paralysis had not been recognized at that time.

I have alluded to some of the known bodily effects of prolonged muscular activity, prolonged loss of sleep and exhaustion, associated with starvation and thirst, noise, fear and other emotions, blast and wounds. The effects of exhaustion, starvation, thirst, noise and loss of

111. Claude, H.; Vigouroux, A., and Lhermitte, J.: Sur certaines dystrophies musculaires du type myopathique consécutives aux traumatismes de guerre, *Presse méd.* **23**:393-396, 1915.

112. Bénisty (Mme.), A.: Treatment and Repair of Nerve Lesions, London, University of London Press, 1918, p. 131.

113. Lhermitte, J.: Les paralysies amyotrophiques dissociées du plexus brachial à type supérieur consécutives à la sérothérapie antitétanique, *Gaz. d. hôp.* **92**: 1053-1056, 1919.

114. Kraus, W. M., and Chaney, L. B.: Serum Disease of the Nervous System: Report of Three Cases, *Arch. Neurol. & Psychiat.* **37**:1034-1047 (May) 1937.

sleep have all been found in themselves, and while their resulting bodily responses are, in effect, not to be associated with evidence of psycho-neurosis, particularly hysteria, fear and similar emotions militate against, rather than encourage, the development of hysteria while the conditions evoking these emotions persist.

Although there is considerable evidence of the physical disturbance resulting from blast, varying from disintegration to the minor, at times even unrecognizable, sequelae, neuroses do not develop in all men subjected to blast. Except for the immediate psychic symptoms following blast, the symptoms of the neuroses subsequently developing are, for the most part, indistinguishable from those originating from circumstances outside a battlefield. The neuroses developing after blast are as readily treated with success as those originating behind the lines.

Large numbers of men who sustained trivial wounds to their extremities did not show any so-called physiopathic reflex nervous disturbances. In fact, I saw only a few cases, and from the absence of reports in the literature of the United States, apparently other observers likewise observed no great numbers. In some of the reported cases, psychotherapy was effective in the treatment of contracture and paralysis, if not of the vasomotor and thermal disturbances.

Nevertheless, I do not know the effect of all these environmental changes, either alone or in combination, on the body of man. I do not know whether such effects, some evanescent, some more permanent, influence the subsequent responses of men—perhaps only some men are affected, certain men in one manner and others in another—and if they do I do not know how. I do not know of any one who does.

I hope, and have reason to expect, that those who will have the opportunity of studying these environmental changes, some of which are peculiar to war, will be able, with the assistance of new methods of investigation and the advance of science generally, to make discoveries that will aid in explaining their effects, in addition to only naming them.

Northwestern University Medical School.

EFFECT OF AUTONOMIC DRUGS ON CEREBRO- SPINAL FLUID PRESSURE IN SCHIZO- PHRENIC AND OTHER PSYCHOSES

I. EFFECT OF HISTAMINE

EMERICK FRIEDMAN, M.D.

AND

THOMAS THALE, M.D.

NORWICH, CONN.

In an attempt to relate the biologic structure of schizophrenic psychoses to sluggishness or limited reactivity of the cerebral vasomotor system, it was believed quite possible to utilize routine lumbar punctures to study the comparative effect of autonomic drugs on the cerebrospinal fluid pressure. Histamine was the first autonomic drug thus employed because of its well known vasodilator action in human and in animal subjects.

PROCEDURE

Studies of the spinal fluid pressure were made on 63 patients with schizophrenia and 68 patients with other types of psychoses. The groups were comparable as to age and duration of hospitalization. Lumbar pressures were measured before and after withdrawal of 10 cc. of spinal fluid with the patient in the lateral recumbent position. Pressures were then recorded ten minutes after subcutaneous injection of 1 ampule of histamine phosphate (1 mg. per cubic centimeter). A third series of recordings was made after another withdrawal of 10 cc. of fluid. Levels of pressure were read in all cases to the nearest 10 mm. mark.

As positive pressure controls, a mixed group of 20 patients was studied as already described except that injection of histamine was omitted. The lack of pressure change in ten minutes in this group indicated that the responses in the 131 cases in the first group were due to histamine rather than to compensatory phenomena.

RESULTS

The table presents the statistical summary of the changes of cerebrospinal fluid pressure in response to histamine in schizophrenic patients as compared with the observations on nonschizophrenic patients.

From the Norwich State Hospital.

The cases making up this study were from both the Norwich State Hospital and the Metropolitan State Hospital, Waltham, Mass.

This paper was read in part at a meeting of the Boston Society of Psychiatry and Neurology, May 16, 1940. An abstract, with discussion, appeared in the November 1940 issue of the ARCHIVES, page 1148.

1. The critical ratios of the changes in pressure following withdrawal of fluid were very high, which shows that the fall in pressure was related to the withdrawal of fluid—a fact clinically accepted. It is noted that withdrawal of 10 cc. of spinal fluid caused the pressure to fall more in the nonschizophrenic group. The difference between the groups was 12.7 mm., with a critical ratio of 2.8, which is suggestively significant.

2. Critical ratios of rises in cerebrospinal fluid pressure following injection of histamine were over 3 for both the schizophrenic and the

Responses of Cerebrospinal Fluid Pressure in Schizophrenic and in Nonschizophrenic Patients to Withdrawal of Fluid and Subcutaneous Injection of Histamine Phosphate

	Groups of Patients	
	Non-schizophrenic	Schizophrenic
Number of patients.....	68	63
Mean initial pressure, mm.....	142.8	149.7
Standard deviation of mean, mm.....	± 5.28	± 5.5
Difference between groups, mm.....		6.9
Critical ratio of difference*.....		0.96
Mean pressure after withdrawal of 10 cc. of fluid, mm.....	102.7	122.3
Standard deviation of mean, mm.....	± 5.28	± 7.4
Mean change (fall) after withdrawal of 10 cc. of fluid, mm.....	40.1	27.4
Standard deviation of mean change, mm.....	± 3.27	± 3.44
Critical ratio of change.....	12.3	7.0
Difference between change in groups, mm.....		12.7
Critical ratio of difference.....		2.8
Mean pressure after histamine, mm.....	143.4	140.9
Standard deviation of mean, mm.....	± 6.6	± 7.0
Mean change (rise) produced by histamine, mm.....	40.7	18.6
Standard deviation of mean change, mm.....	± 3.27	± 5.02
Critical ratio of change.....	12.3	3.7
Difference between change in groups, mm.....		22.1
Critical ratio of difference.....		3.7

$$* \text{ Critical ratio: } \frac{\text{Change}}{\text{Standard deviation of change}}$$

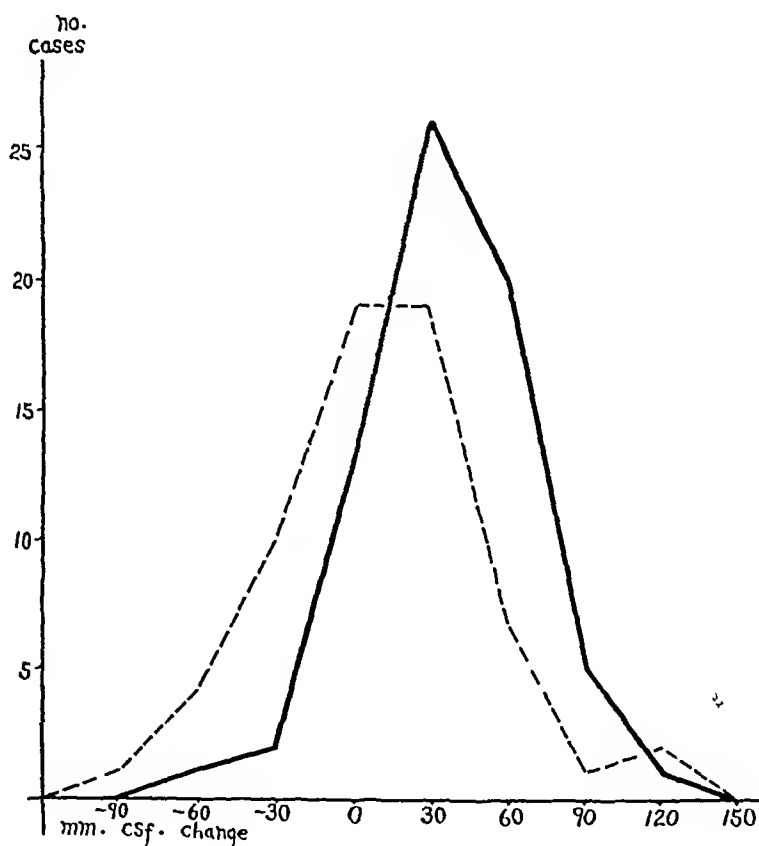
nonschizophrenic group, which shows that such rises could not be ascribed to random variations in pressure. The rise in pressure following injection of histamine was 22.1 mm. higher in the nonschizophrenic than in the schizophrenic group. This difference had a critical ratio of 3.7, which indicates the reliability of this difference.

3. The figure shows the distribution of pressure changes following histamine. The tendency toward greater reactivity of the nonschizophrenic patients is quite apparent.

The dispersions (standard deviations) for the schizophrenic group are somewhat greater than those for the nonschizophrenic group for all readings. This may be an indication of the lack of homogeneity of the

schizophrenic group, even when compared with a mixed group of patients with a number of other psychoses.

One is struck by the relative nonreactivity of the cerebrospinal fluid pressure to histamine in the schizophrenic group. After withdrawal of the first 10 cc. of fluid the schizophrenic group had less fall in pressure—or had a more efficient adjustment of the cerebrospinal fluid dynamics. In other words, the schizophrenic patients responded with less of a fall in pressure to withdrawal of fluid and, on the other hand, with less of a rise in pressure to histamine.



Distribution curves showing changes in cerebrospinal fluid pressure in 63 schizophrenic patients and in 68 patients with psychoses other than schizophrenia following subcutaneous injection of histamine phosphate. The horizontal line expresses in millimeters of cerebrospinal fluid, changes in cerebrospinal fluid pressure; the vertical line indicates the number of cases. The continuous line represents nonschizophrenic and the broken line schizophrenic patients.

The latter response could be expressed in a different manner. It was found that almost 75 per cent of the nonschizophrenic patients responded to histamine with rises of 30 mm. or more, while only a little over 40 per cent of the schizophrenic patients reacted to this extent. Furthermore, while, practically, 20 per cent of the schizophrenic patients displayed a fall in pressure after injection of histamine, only 7 per cent of the nonschizophrenic patients showed such a fall.

COMMENT

The explanation for the relatively lesser response in cerebrospinal fluid pressure of the schizophrenic patients to histamine is possible only on a theoretic basis.

Forbes and associates,¹ Loman and Myerson² and Weiss and associates,³ after investigation of the cerebrovascular action of histamine in human subjects and in animals, concluded that histamine brings about direct vasodilatation of the cerebral and pial vessels. The fact that histamine acts on the peripheral vascular branches regardless of their nerve supply and that various autonomic organs differ in their responses to histamine, according to Sollmann,⁴ makes this type of study fruitful in an attempt to relate the psychosomatic pattern of schizophrenia to autonomic rigidity or limited reactivity.

In our cases, the general factors of prolonged hypokinesia and habituation to a sedentary existence did not seem to play an important role. Practically all of the patients included in this study were of the chronic institutionalized type, regardless of their diagnoses. All of the patients included in this series were cooperative in the tests—data on combative, overtalkative and restless patients were excluded.

The relatively diminished response of the cerebrovascular mechanism to histamine in schizophrenic patients may be related to similar observations on the autonomic nervous system reported by other workers (bibliography collected by Lewis⁵). The schizophrenic patients in this study who did display a significant response to histamine seemed on gross observation to be of the paranoid type and, furthermore, to "show no signs of deterioration." Statistically, however, the number of patients studied is as yet insufficient to constitute a valid test of this opinion.

SUMMARY

A method of studying the reactivity of the cerebrospinal fluid pressure to autonomic drugs is described. This method was employed in comparing the cerebrovascular responses of 63 schizophrenic patients

1. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: The Action of Histamine, *Am. J. Physiol.* **89**:266-272, 1929.

2. Loman, J., and Myerson, A.: The Action of Certain Drugs on the Cerebrospinal Fluid and on the Internal Jugular Venous and Systemic Arterial Pressures of Man, *Arch. Neurol. & Psychiat.* **27**:1226-1244 (May) 1932.

3. Weiss, S.; Lennox, W. G., and Robb, G. P.: The Dilator Effect of Histamine on the Cerebral Vessels in Man, *Proc. Soc. Exper. Biol. & Med.* **26**:706-707, 1929.

4. Sollmann, T.: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936, pp. 440-444.

5. Lewis, N. D. C.: Research in Dementia Praecox, New York, National Committee for Mental Hygiene, 1936, pp. 131-210.

and those of 68 patients with nonschizophrenic psychoses. Histamine was used in this first study because of its well known somatic action.

Significantly smaller response of the cerebrospinal fluid pressure to subcutaneous injections of histamine was noted in the schizophrenic patients. This was associated with another observation, namely, that the schizophrenic patients tended to show less decrease of cerebrospinal fluid pressure after withdrawal of 10 cc. of fluid.

This study indicated that schizophrenia may be characterized by a relatively limited cerebrovascular reactivity to administration of histamine.

Norwich State Hospital.

Clinical, Technical and Occasional Notes

ELECTRICAL SKIN RESISTANCE TECHNIC USED TO MAP AREAS OF SKIN AFFECTED BY SYMPATHECTOMY AND BY OTHER SURGICAL OR FUNCTIONAL FACTORS

FRED G. WHELAN, B.E., AND CURT P. RICHTER, PH.D., BALTIMORE

During the past two years we have shown by means of the electrical skin resistance method, or measurement of the resistance offered to passage of minute direct current through the skin, (1) that areas of skin affected by upper thoracic or lumbar sympathectomy can be sharply defined on any part of the body, such areas having an abnormally high resistance; (2) that the patterns of these areas closely correspond to the sensory dermatomes and to areas which do not sweat, as was demonstrated by the Minor starch-iodine-sweating test (Richter and Woodruff¹); (3) that areas affected by injection of procaine or alcohol into the sympathetic chain can be quickly and sharply defined, often within a few minutes after injection (Shumacker²), and (4) that the skin of normal persons manifests rather constant and hitherto entirely unsuspected areas of low electrical skin resistance on the face, hands, feet, axillas and antecubital fossae. The size and shape of these areas vary with sleep, external temperature, hair distribution and metabolic activity (Richter and Woodruff³). For example, the facial pattern which under ordinary conditions includes the eyes, nose and mouth becomes constricted to include only the mouth under conditions of cold and during sleep.

A simplification of the nonpolarizable electrodes ordinarily used for studies of skin resistance has made it possible to map these areas of high and low resistance on the skin. Along with other workers, we had long believed that a paste or some other substance was necessary to make contact between the metal of the electrodes and the skin and

This work was carried on under a grant from the John and Mary R. Markle Foundation.

From the Departments of Electrical Engineering and Psychiatry, Johns Hopkins University.

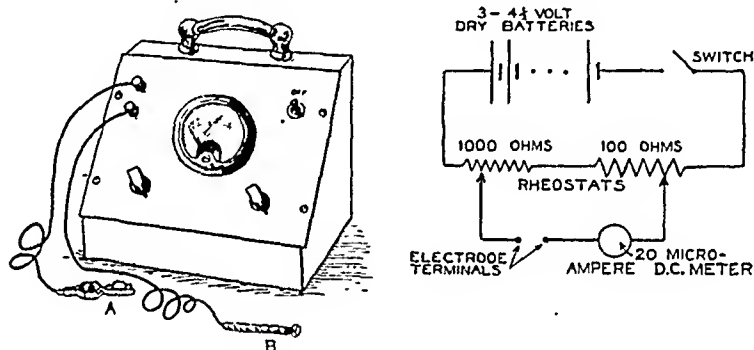
1. Richter, C. P., and Woodruff, B. G.: Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, *Surgery* **10**:957-970, 1941.

2. Shumacker, H. B., Jr.: The Value of Skin Resistance Studies in Determining the Accuracy of Procaine Injections of the Sympathetic Nerves, *Surgery* **11**:949 (June) 1942.

3. Richter, C. P., and Woodruff, B. G.: Facial Patterns of Electrical Skin Resistance—Their Relation to Sleep, External Temperature, Hair Distribution, Sensory Dermatomes and Skin Disease, *Bull. Johns Hopkins Hosp.* **70**:442-459 (May) 1942.

that without such a substance the electrode would become polarized and thus invalidate the results. The substance which we had used for many years was a paste made of kaolin and saturated solution of zinc sulfate (Richter⁴). When the zinc electrode, covered with the kaolin paste, was moved from place to place on the skin, the entire body quickly became covered with paste. Repeated readings over the same area gave ever lower readings on account of the stimulating effect of the paste itself. Contrary to the current belief, we found that a zinc disk without any paste at all gave excellent results. Such an electrode could be moved freely over the skin of the body, and readings could be made indefinitely without changing the level of the skin resistance.

A brief description of the technic will suffice for present purposes. The figure shows dermatometer and the electrodes constructed for this work. One electrode (*A*), a $\frac{1}{2}$ inch (1.3 cm.) disk attached to a clip, is fastened over an ear lobe. It consists of a $\frac{1}{2}$ inch zinc disk soldered to the inner surface of one of the two flat arms of a specially built pinch clip about 3 inches (7.5 cm.) long. The arm which carries the disk ends in a small hook bent in toward the



Dermatometer and electrodes used to measure skin resistance.

other arm. The hook placed over the antitragus prevents dislodgement of the clip when the subject moves about. The other electrode (*B*) consists of a $\frac{1}{4}$ inch (0.6 cm.) zinc disk soldered at right angles to the end of an insulated $\frac{1}{8}$ inch (0.3 cm.) zinc rod 3 inches (7.5 cm.) long. With this rod as a handle the flat surface of the zinc disk can be applied to the skin on any part of the body. The electrodes are connected to a box which contains an ammeter, two rheostats, a switch and three $4\frac{1}{2}$ volt, dry cell radio batteries. The portable box and all of the equipment can be used at the bedside, in the operating room and in the laboratory. The figure also shows the wiring plan.

In examination of a sympathectomized patient the movable electrode is placed over the affected area, which always has an abnormally high resistance. The rheostats are then set so that only a very small current flows through the body between the electrodes, indicated by a small deflection of the ammeter pointer. The electrode is then moved in small steps toward the normal areas of the skin. A sudden full deflection of the pointer entirely across the dial of the ammeter indicates the arrival over a normal area. If the electrode is moved back and

4. Richter, C. P.: The Sweat Glands Studied by the Electrical Resistance Method, *Am. J. Physiol.* 68:147, 1924.

forth in progressively smaller steps between the affected and the normal area, a point of demarcation can be determined. If successive points of demarcation are linked together, a line is obtained the ends of which ultimately join to form a boundary of the patterns of low and high skin resistance. The line of demarcation is usually sharp, rarely being more than $\frac{1}{8}$ inch (0.3 cm.) wide. The areas for the face and those for the hands are determined by essentially the same method.

This technic is now being used to map areas affected by injuries of peripheral nerves and to follow the process of regeneration of the sutured nerves, as well as to map areas of referred pain and areas affected by tumors of the spinal cord or other destructive processes.

Johns Hopkins University.

Obituaries

STEPHEN WALTER RANSON, M.D.

1880-1942

Stephen Walter Ranson, professor of neurology and director of the Neurological Institute at the Northwestern University Medical School, died of coronary thrombosis at Chicago on Aug. 30, 1942, two days after he had reached his sixty-second birthday. He is survived by his wife, Tessie, and by 3 children, Capt. Stephen W. Ranson, Mrs. Margaret Jane Lacy and Miss Mary Elizabeth Ranson.

Dr. Ranson was born at Dodge Center, Minn., on Aug. 28, 1880 and was the son of Dr. Stephen William and Mary Elizabeth Foster Ranson, who were of English and Welsh extraction. Dodge Center was his home until he entered the University of Minnesota, in 1898. The son of a physician, he grew up in a family of 6 children, 3 daughters and 3 sons, of which he was the youngest. It is interesting to note that of this family, 3 became physicians and 1 received the degree of Doctor of Philosophy in psychology. From early childhood Dr. Ranson exhibited a strong sense of responsibility and initiative in doing important things without direction. He finished high school in three years. After his entrance into the University of Minnesota, he came under the influence of Prof. J. B. Johnston, who developed in him an intense interest in the nervous system. During the summer following his first year, when he was just 19 years old, he set up a laboratory in the barn on the family property in Dodge Center and started experiments on cats, his favorites for experiments throughout his life. He did the same thing the following summer and then, subsequent to the end of his third year, he transferred to the University of Chicago. In 1902, he received the degree of Bachelor of Arts from the University of Minnesota and entered graduate work at the University of Chicago. Here he worked under the direction of the late Prof. H. H. Donaldson. He received the degree of Master of Science in 1903 and that of Doctor of Philosophy in 1905. His dissertation was entitled "Retrograde Degeneration in the Spinal Nerves." In 1904, while still a graduate student, he went with the late Prof. A. C. Eycleshymer to the St. Louis University School of Medicine and helped with the work in the department of anatomy there for part of the year. He served as a fellow in neurology at the University of Chicago in 1904-1906, and in 1907 he was awarded the degree of Doctor of Medicine from Rush Medical College. After a year's internship at the Cook County Hos-

pital, he had planned to establish a practice in Chicago. However, Prof. Arthur W. Meyer, who was professor of anatomy at Northwestern University Medical School during the year 1908-1909, induced Dr. Ranson to take an appointment as associate in anatomy. When Dr.



STEPHEN WALTER RANSON, M.D.
1880-1942

Meyer left for Stanford University the following year, Ranson took two important steps. He decided to carve out his career in anatomy and accepted an appointment as assistant professor and acting head of the department. On Aug. 18, 1909 he married Miss Tessie Grier Rowland, of Oak Park, Ill, who entered into the spirit of his career

and made his life with his family a most pleasant one, in a home that radiated hospitality. In 1910, he became associate professor and then, in 1912, professor and head of the department of anatomy at Northwestern University, where he served for the subsequent twelve years. He spent the year 1910-1911 at Freiburg, Germany, in Professor Wiedersheim's laboratory. During these years, he accomplished much in the face of obstacles. The medical school was then located on the south side of Chicago, and the quarters for the department were inadequate, as was the budget. In addition to carrying a heavy teaching load in a most conscientious fashion and to conducting many important researches, he was a leader in the advancement of scientific medicine in his institution.

In 1924, he went to the Washington University School of Medicine, in St. Louis, to become professor of neuroanatomy and head of the department of neuroanatomy and histology. He was extremely happy with his opportunity there, which offered him a reduced teaching load and excellent facilities for research. However, Northwestern University had never become reconciled to his leaving and induced him to return to the Northwestern University Medical School on Feb. 1, 1928, to become professor of neurology and director of the newly formed Neurological Institute there. He had envisioned such a development in neurology and had spent the summer of 1926 at Queen's Square Hospital, in London, with Gordon Holmes and Kinnier Wilson in following the clinical material there and the methods of treatment. He remained at Northwestern University the rest of his life, where his influence was felt throughout the institution, but he devoted himself mainly to building, developing and maintaining one of the most productive schools of neurology that has ever existed. The first annual volume appeared in 1929, and each year since the work of the Institute has been presented and collected in such a volume. The total is a most formidable array of important contributions. His task was not an easy one, but in his quiet manner he met the problems as they arose. He felt keenly his responsibility to make this institute a successful venture, and he bent his complete energy to attaining this end.

His own research is recorded in a bibliography of 205 titles¹ and gives expression to his interest in the nervous system from a morphologic and a functional standpoint. Demonstration of the structure of a part of the nervous system was a challenge to him to learn its functional significance. He was the leader of an important school of mammalian neuroanatomy and neurophysiology. He was interested throughout his life in anatomic makeup of the peripheral, cerebrospinal and visceral nervous systems, including degeneration, regeneration and distributions

1. This bibliography has been published by H. W. Magoun (*Quart. Bull., Northwestern Univ. M. School* **16**:304-310, 1942).

of the various types of nerve fibers. His demonstration of unmyelinated nerve fibers, as early as 1909, was made more evident with the introduction of his pyridine-silver technic in 1914, an important modification of one of Cajal's. He observed unmyelinated fibers in large numbers in sensory nerves and devised experiments to show that they mediate pain sensation. Owing to opposition here and in England, Ranson experienced a long, up-hill struggle in securing recognition for this point of view, but later experiments of his own and the cathode ray oscillograph analyses, such as were made by Erlanger, Gasser, Bishop and others, have more than vindicated his earlier work. His recognition of unmyelinated fibers made his histologic analyses of the peripheral visceral nervous system much more complete than previous ones. He analyzed peripheral and central visceral afferent pathways and vasomotor centers in the medulla oblongata and did a review on "Afferent Paths for Visceral Reflexes" in the first volume of *Physiological Reviews*.

For a period of years he worked on the mechanisms involved in postural contractions, or what was then called muscle tonus. He finally convinced himself that there was no postural influence exerted by efferent impulses over dorsal root fibers. This turned his attention to reflex physiology, with a study of spinal reflexes and the regulation of limb reflexes by various levels of integration in the central nervous system. Ranson and his colleagues first became interested in the hypothalamic region through a chance observation that "hypothalamic" animals could walk. The initial interest in this region was for its significance in somatic motor integrations, and it was for their study that Ranson introduced the Horsley-Clarke stereotaxic apparatus into his laboratory in 1930. He had seen this apparatus used in work on the cerebellum in progress under the direction of Dr. Ernest Sachs at Washington University.

After early experiments in refining the technic, establishing anatomic controls and studying somatic motor integration in the midbrain, subthalamus and hypothalamus, he directed the attention of his laboratory toward the analysis of visceral responses elicited by stimulations in this region and of symptoms arising from lesions accurately placed by electrolysis. The precision of observation and anatomic controls extended and greatly amplified the earlier work, such as that of Karplus and Kreidl and of Isenschmid and Krehl, done some twenty years previously. Paper after paper appeared elucidating such problems as the significance of the hypothalamus and the hypophysis in water exchange and the syndrome of diabetes insipidus, and of the hypothalamus in temperature regulation, obesity, sexual function, emotional expression, catalepsy and other abnormal conditions. A review of this work leads to the conclusion that the hypothalamus serves as a level of visceral integra-

tion from which impulses are directed, on the one hand, to the hypophysis, and, on the other, down the brain stem and the spinal cord to activate visceral motor neurons at these different levels. During this time, there were other experiments, such as those on the pathways for pupillary light reflexes and the function of the cerebellum and anatomic and physiologic studies on the corpus striatum. The corpus striatum occupied much of his attention at the last, and this work was particularly enjoyable because his son, Stephen, and his daughter Mary cooperated in it and because it was possible to clarify a number of anatomic ambiguities in this region. A short time before his death, he again turned his attention to problems of nerve regeneration, and he was outlining a new experimental approach to this problem.

That his work was widely recognized is indicated by the lectures he was requested to give: the Weir Mitchell Oration (1934), the Harvey Lecture (1936), the Dunham Lectures (1940) and the Hughlings Jackson Lecture (1941). Volume XX (1940) of the *Association for Research in Nervous and Mental Disease, Proceedings*, entitled "The Hypothalamus and Central Levels of Autonomic Function," contains the following dedication: "In recognition of the distinguished contributions to knowledge of hypothalamic functions made by himself and by the students he has inspired, this meeting of the association is dedicated by the trustees to Stephen Walter Ranson."

In addition to these contributions in the experimental field, Ranson was the author of the textbook, "The Anatomy of the Nervous System," the first edition of which appeared in 1920, and just before his death he had completed the seventh edition. The appearance of this textbook brought the teaching of neuroanatomy to a much higher plane and has been a most important factor in the development of this branch of anatomy in a superior fashion in the United States. It is an expression of his systematic, orderly and thorough approach, and generations of medical students have profited from its use. In the earlier years of his teaching, he taught gross anatomy, as well as neuroanatomy. At Washington University he taught histology and neuroanatomy. He was extremely conscientious as a teacher, and his kindly and sympathetic manner will be remembered by many a student. When he returned to Northwestern University, in 1928, he gave up undergraduate teaching. When one of his associates expressed regret over this, his reply was, "When you have taught as long and as much as I have, you will welcome an opportunity to give it up." He welcomed it, not because of a fundamental dislike for teaching, but because it would give him greater opportunity for his experimental work.

Into the work of his laboratory he attracted many students, both from this country and from abroad, who worked under his direction. He had the happy faculty of stimulating teamwork, an intense interest

in experimental work and the utmost loyalty. He trained many men who now have teaching posts in anatomy and physiology in various institutions. In addition are the men in clinical medicine, not only in neurology and in psychiatry but in pediatrics, surgery, medicine and other specialties, who spent time under his tutelage. His enthusiasm was infectious and his training rigid and demanding, and he has made better physicians of those who were with him. He spent endless time in looking over and sizing up candidates who desired places in his laboratory, because he wanted the best material he could find and because he realized the importance of teamwork and cordial relations on the part of his staff. He used similar discrimination in the choice of his technicians and laboratory attendants. He kept his hand in the experiments, carried his share of the load and gave great attention to the designing of his experimental attack. He was extremely critical and difficult to convince. His publications demonstrate his extreme care for completeness, minutiae and controls. He was a trained morphologist with such strong interests in physiologic significance that he instinctively turned to and developed methods for the study of neurophysiology that have withstood critical appraisal. He had a keen appreciation for the problems of clinical neurology and the implications of his work in this field. However, he did not deviate from his objectives in fundamental problems of morphology and physiology in his attack on the nervous system.

He was a fellow of the American Association for the Advancement of Science and a member of the National Academy of Science, the American Neurological Association, the American Physiological Society and the American Association of Anatomists, of which he was president from 1938-1940. He served for a number of years on the Committee on Nomenclature of the American Association of Anatomists, and he was a member of the editorial board of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. His medical fraternity, Phi Beta Pi, established an annual lectureship in his honor at the Northwestern University Medical School in 1929. He was elected to Alpha Omega Alpha while an undergraduate medical student.

Dr. Ranson was a dignified, modest and retiring man, who felt keenly his responsibility for leadership for the advancement of knowledge in neurologic sciences. There was no place for sham, bluff or front in his makeup, and he easily recognized it in others. He did not hesitate to question dogma and didactic authorities and to stand his ground against attack and criticism. He was a worthy opponent, but a fair one, in any argument. He could dissociate evidence from the fluency of presentation and would probe beneath the surface and veneer of salesmanship for the real facts. He worked diligently all his life, even to the detriment of his own health in later years. He nursed a gastric ulcer for the last ten years of his life. His interest was in estab-

lishing factual evidence rather than in selling himself. He was a devoted husband and father, who found time to enjoy and contribute to the family circle. He was very pleased that his son, Stephen, chose medicine as a profession and that he secured a thorough training for clinical neurology. Likewise, his daughter Mary showed proficiency in her work with him in the laboratory. He was a proud grandfather and exhibited great interest in his three grandchildren.

The students who passed through his laboratory were extremely loyal to him and appreciated the fatherly interest he took in their scientific development and their personal problems. They continued to communicate and visit with him for help and advice long after they had left his laboratory. He always made them feel welcome. There was a spirit of give and take, of fellowship and of dignified respect, without any exhibition of austere domination. He was a leader of strength and high ideals, whose accomplishments will live through time and whose influence will be continued by his students and associates.

JOSEPH C. HINSEY, PH.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

A CYTOARCHITECTURAL STUDY OF THE SHEEP CORTEX. JERZY E. ROSE, *J. Comp. Neurol.* **76**:1 (Feb.) 1942.

Rose has divided the cerebral cortex of the sheep into *holocortex septemstratificatus*, *bicortex*, *mesocortex*, *holocortex bistratificatus*, *schizocortex* and *semicortex*. Each of these cortices lie further subdivides into regions and into areas on the bases of morphologic and topographic properties.

ADDISON, Philadelphia.

THE CEREBRAL CORTEX IN THE GROUNDHOG (*MARMOTA MONAX*) AND THE DEER MOUSE (*PEROMYSCUS MANICULATUS*). H. CHANDLER ELLIOTT, *J. Comp. Neurol.* **76**:75 (Feb.) 1942.

Two dimensional maps are presented to show the extent of the areas of the cerebral cortex of the groundhog and of the deer mouse. The occipital cortex of the groundhog and the temporal cortex of the deer mouse show a greater development than those of other rodents. The parietal area is large in both species, but the frontal area is small in the groundhog, as it is in other large rodents.

ADDISON, Philadelphia.

Physiology and Biochemistry

EFFECT OF AMOUNTS OF SINGLE VITAMINS OF THE B GROUP UPON RATS DEFICIENT IN OTHER VITAMINS. KLAUS UNNA and JOSEPHINE D. CLARK, *Am. J. M. Sc.* **204**:364 (Sept.) 1942.

Unna and Clark studied the manner in which the course and the manifestations of deficiencies due to the lack of one factor of the vitamin B complex may be influenced by the prolonged administration of excessive amounts of the various other members of the B group. Experiments were carried out on 920 male albino rats. At 3 weeks of age the rats were placed on highly purified diets deficient either in the entire vitamin B complex or in individual factors, such as riboflavin, pyridoxine or pantothenic acid. The rats maintained on the various diets were divided into series of 20 each. Each series received a daily supplement of one vitamin in an excessive amount. The rats were subdivided into three groups of 20 each. One group received no supplement; the other two groups were fed daily 10 micrograms and 1 mg. of thiamine hydrochloride respectively. The rats receiving no supplement declined in weight, whereas the rats receiving either 10 micrograms or 1 mg. of thiamine hydrochloride maintained their weight for a period of six weeks.

Three hundred and sixty rats, divided in three equal series were placed on diets deficient in riboflavin. One series received no riboflavin. The other two were given a daily supplement of 2 and 10 micrograms of riboflavin respectively. Each of the three series was subdivided into one group of 40 animals receiving no further supplement and four groups of 20 animals each receiving excessive amounts of thiamine hydrochloride (1 mg.), nicotinamide (10 mg.), pyridoxine (1 mg.) and pantothenic acid (10 mg.) respectively. All animals receiving no riboflavin gained about 13 Gm. during the first three weeks, after which period their weights became stationary. The additional feeding of 2 micrograms of

riboflavin per rat per day to the second series of rats on the riboflavin-free diet resulted in average gains in weight of about 40 to 50 Gm. for a period of ten weeks.

Three hundred rats, divided into three equal series, were placed on diets deficient in pantothenic acid. One series of animals received no pantothenic acid; another series of animals received a daily supplement of 25 micrograms of calcium pantothenate per rat, an amount insufficient for optimum growth. The third series was given 100 micrograms of calcium pantothenate. The three series of animals were subdivided into three groups of 20 each and were fed large daily doses of single vitamins. The animals of the first series, which received no pantothenic acid, gained between 20 and 30 Gm. during the first three weeks. In the second series of animals, which received a daily supplement of 25 micrograms of calcium pantothenate, no difference in the rate of growth of the various groups was noted. The third series gained at a rate of approximately 3 Gm. per rat per day. In this series there was no difference in the rate of growth between the control and the other groups receiving large amounts of other vitamins.

Two hundred rats were placed on a diet free from pyridoxine. A group of 100 animals receiving no further supplement served as a control for two groups of 50 rats each which were given a daily supplement of 1 mg. of thiamine hydrochloride and 10 mg. of calcium pantothenate respectively. No difference was observed between the rates of growth of the three groups. The authors conclude that prolonged administration of large amounts of individual vitamin of the B group to rats subsisting on diets either entirely free from or partly deficient in one or more factors of the vitamin B complex failed to aggravate the manifestations of the deficiency state.

MICHAELS, Boston.

A STUDY OF THIAMINE DEFICIENCY IN SWINE. MAXWELL M. WINTROBE, HAROLD J. STEIN, MITCHELL H. MILLER, RICHARD H. FOLLIS JR., VICTOR NAJJAR and STEWART HUMPHREYS, *Bull. Johns Hopkins Hosp.* **71**:141 (Sept.) 1942.

Pigs, about 3 weeks old, were fed a simple diet poor in the vitamin B complex. Acute and relatively chronic states of thiamine deficiency were produced by adding no, or only inadequate quantities of, thiamine hydrochloride.

The outstanding symptoms of thiamine deficiency were failure of appetite, vomiting, dyspnea, cyanosis and sudden death; poor growth was a less striking sign. When death occurred, the terminal symptoms were those of acute severe cardiac failure. No edema other than that of the lungs was ever noted. Once vomiting or anorexia had appeared, symptoms of cardiac failure often developed suddenly and unexpected death sometimes occurred. In all the animals which died after thiamine deficiency focal necrosis of the myocardium was observed. There were no neurologic symptoms or degenerative changes of the nervous system.

The pyruvic acid content of the blood and the thiamine in the urine were measured. These observations suggest that the urinary thiamine excretion reflects only the immediately preceding thiamine intake. The thiamine tolerance test is a useful measure of thiamine deficiency states. The pyruvic acid content of the blood, although influenced by factors in addition to the thiamine and the carbohydrate intake, was found to be correlated with the onset and the severity of symptoms of thiamine deficiency. More useful than a single determination of the pyruvic acid level of the blood, however, was a comparison of the values before and after the administration of a measured amount of dextrose.

PRICE, Philadelphia.

APHASIA AFTER MAJOR TEMPORAL LOBECTOMY. AIDAN A. RANEY, ARNOLD P. FRIEDMAN and J. M. NIELSEN, *Bull. Los Angeles Neurol. Soc.* **7**:154 (Sept.) 1942.

The authors report a case of aphasia following major temporal lobectomy for a large left temporo-occipital neoplasm. A study of the language function made

three weeks after operation showed that the patient's language formulation was completely lost. She had no ability to read or write and had slight retention of ability to comprehend spoken language. She was able to recognize objects and colors and had complete right homonymous hemianopia.

LESKO, Bridgeport, Conn.

NICOTINIC ACID DEFICIENCY STUDIES IN DOGS. A. E. SCHAEFER, J. M. MCKIBBIN and C. A. ELVEHJEM, *J. Biol. Chem.* **144**:679, 1942.

Uncomplicated nicotinic acid deficiency in young dogs may be produced on a highly purified casein-sucrose ration supplemented with thiamine, riboflavin, pyridoxine, pantothenic acid and choline. This ration seems suitable for the assay of food materials for their nicotinic acid content. The requirement of nicotinic acid, as calculated by single dose feedings, for adult dogs ranges from 200 to 225 micrograms per kilogram of body weight per day, and for young growing puppies it ranges from 250 to 365 micrograms per kilogram. Feeding sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) inhibits the response of the nicotinic acid-deficient dog to nicotinic acid, nicotinamide, dried liver and liver extract powder. This inhibition is overcome by feeding of fresh liver.

PAGE, Indianapolis.

ARTERIAL AND CEREBRAL VENOUS BLOOD. L. F. NIMS, E. L. GIBBS and W. G. LENNOX, *J. Biol. Chem.* **145**:189, 1942.

Rapid alteration of the carbon dioxide content of the arterial blood in man and in anesthetized monkeys modifies both the frequency and the amplitude of the electrical potentials obtained from the cerebral cortex. Chemical examination of the internal jugular venous blood of healthy young men, when rapid increases or decreases of carbon dioxide in the arterial blood are produced, reveals the presence of effective mechanisms which serve to protect the brain from alterations of its acid-base balance. A direct relation between the inorganic phosphorus and the carbon dioxide level of the blood and an inverse relation between the lactic acid and the carbon dioxide level have been found during changes in carbon dioxide concentration of the arterial blood when these alterations are produced by breathing carbon dioxide-enriched air and by pulmonary overventilation.

PAGE, Indianapolis.

AUTONOMIC RESPONSES TO ELECTRICAL STIMULATION OF THE FOREBRAIN AND MIDBRAIN WITH SPECIAL REFERENCE TO THE PUPIL. ROBERT HODES and H. W. MAGOUN, *J. Comp. Neurol.* **76**:169 (Feb.) 1942.

By means of the Horsley-Clarke technic Hodes and Magoun stimulated the forebrain and the midbrain of 40 cats anesthetized with chloralose (a compound of chloral hydrate and dextrose) or ethyl carbamate by a condenser discharge of a constant frequency of 120 per second. Stimulatory effects on the sympathetically or parasympathetically denervated iris, the nictitating membrane, piloerection on the tail and the blood pressure were observed. The areas stimulated were mapped on outline drawings. Excitor regions for the sympathectomized iris were found rostral to the anterior commissure and extended as far caudally as the level of the superior colliculus. Excitor regions for the parasympathectomized iris, the nictitating membrane and piloerection extended from the level of the optic chiasm without interruption through the hypothalamus and passed into the midbrain by way of the periventricular fibers and fibers running caudally into the tegmentum from the lateral hypothalamic area. The effects on blood pressure were practically identical with those previously reported.

FRASER, Philadelphia.

RELATION OF FIBRILLATION TO ACETYLCHOLINE AND POTASSIUM SENSITIVITY IN DENERVATED SKELETAL MUSCLE. J. W. MAGLADERY and D. Y. SOLANDT, *J. Neurophysiol.* **5**:357 (Sept.) 1942.

Denervation rendered skeletal muscle much more sensitive to acetylcholine and, to a less degree, to potassium chloride. Small concentrations of these agents, when injected intra-arterially, produced action potentials comparable to and superimposed on those of fibrillation. This excitation was abolished by quinidine in doses which would arrest fibrillation. It was suggested, therefore, that the fibrillation seen in skeletal muscle after denervation of the lower motor neuron arose from increased sensitivity of denervated muscle to chemically induced excitation. The present experiments indicated that acetylcholine, potassium or both might be the usual causative agent or agents.

ALPERS, Philadelphia.

EFFECT OF ALCOHOL IN EXPERIMENTAL LIVER CIRRHOSIS. J. V. LOWRY, L. L. ASHBURN, FLOYD S. DAFT and W. H. SEBRELL, *Quart. J. Stud. on Alcohol* **3**:168 (Sept.) 1942.

The authors present evidence to show that cirrhosis of the liver may be produced in rats by dietary deficiency without the use of alcohol. However, when alcohol was substituted for drinking water, the hepatic cirrhosis was usually more severe. The action of the alcohol in these cases is not clear, but it is suggested that alcohol acts by more complex mechanisms than direct toxicity.

LESKO, Bridgeport, Conn.

CHEMICAL CHANGES IN THE BLOOD AND THE OCCURRENCE OF UREMIA FOLLOWING HEAD INJURY. J. N. CUMINGS, *J. Neurol. & Psychiat.* **5**:40 (Jan.-April) 1942.

Of 25 patients with injury to the head, Cumings found no significant changes in the chemical constituents of the blood other than a raised inorganic phosphate content in persons with severe cerebral lesions. In 17 other patients with head injury both the blood and the urine were studied biochemically. Of this group, uremia developed in 4 patients and the urea and phosphate levels of the blood were increased, with a normal volume of urine but with a high excretion of urea in an acid urine. Autopsy on 2 of these patients revealed evidence of renal lesions which differed from those in cases of traumatic anuria following crush injuries of the limbs. There were alterations in the chemical content of phosphate and uric acid in the kidneys of the 2 patients who died of uremia. It is not known whether the underlying mechanism is that associated with damaged cerebral tissue or with some renal abnormality. Alkalis produced clinical improvement in 1 patient with a raised urea content of the blood.

N. MALAMUD, Ann Arbor, Mich.

THE EFFECT OF HYPERTONIC GLUCOSE SOLUTIONS ON THE INFLOW OF NORMAL SALINE SOLUTION INTO THE SUBARACHNOID SPACE OF THE DOG. T. H. B. BEDFORD, *J. Physiol.* **101**:106, 1942.

Hypertonic (25 or 50 per cent) solution of dextrose, as well as hypertonic solutions of levulose and sodium chloride, caused an increase in cerebrospinal fluid pressure, with a corresponding decrease in the rate of inflow of physiologic solution of sodium chloride under constant pressure into the subarachnoid space after a brief interval during which the opposite effect was observed. This interval was longer when sodium chloride was used. Edema and swelling of the brain were a frequent result, especially after administration of dextrose. The author concludes that this is the most characteristic result of the intravenous administration of a hypertonic solution of dextrose in the dog.

THOMAS, Philadelphia.

THE CHOLINERGIC NATURE OF THE NERVES TO THE ELECTRIC ORGAN OF THE TORPEDO. W. FELDBERG and A. FESSARD, *J. Physiol.* **101**:200, 1942.

Feldberg and Fessard conclude that the nerves to the electric organ of the torpedo are cholinergic on the basis of the following evidence: (1) The organ contains between 40 and 100 mg. of acetylcholine per gram of fresh tissue; (2) the acetylcholine content of the perfusion fluid is increased by stimulation of the nerves to the perfused organ; (3) intra-arterial injection of acetylcholine has an electrogenic effect, and (4) physostigmine increases the sensitivity of the organ to intra-arterial acetylcholine.

THOMAS, Philadelphia.

Meninges and Blood Vessels

THE PROGNOSIS OF PNEUMOCOCCIC MENINGITIS TREATED WITH CHEMOTHERAPY. G. HOLLANDER, *Am. J. M. Sc.* **203**:370 (March) 1942.

Hollander reviews 260 reported cases of pneumococcic meningitis in which chemotherapy, with or without specific serum was employed, in an attempt to evaluate the effectiveness of each of the therapeutic agents, alone and combined. In 160 cases in which chemotherapy alone was employed, sulfapyridine (2-[para-aminobenzenesulfonamido]-pyridine) proved to be a more efficacious drug than sulfanilamide. The percentages of recovery with sulfapyridine therapy alone and with sulfapyridine-serum therapy are the same (58 per cent). The irregularity of absorption of the drug leads to difficulty in estimating the dosage. The efficiency of the sulfanilamide drugs is relatively unimpaired by the type of the pneumococcus involved. In cases of meningitis due to types III and V the combined sulfapyridine-serum therapy seems to be indicated. The prognosis for pneumococcic meningitis secondary to pneumonia is poor. Combined treatment with sulfapyridine and serum gives the best prognosis in the age period between 10 and 20 years, in which almost one third of the recoveries have occurred. The prognosis is favorable if the cerebrospinal fluid is sterilized within four days after the administration of sulfapyridine. Sulfapyridine is the drug of choice in the treatment of pneumococcic meningitis.

MICHAELS, Boston.

TORULA MENINGITIS. WESLEY N. WARVI and RULON W. RAWSON, *Arch. Int. Med.* **69**:90 (Jan.) 1942.

Warvi and Rawson call attention to the frequency with which torula meningitis is associated with Hodgkin's disease. Seventy-eight cases of torula meningitis have been noted to date. Torula is a yeastlike organism and is only rarely pathogenic for man. It differs from a true yeast in that it does not produce endospores and forms myceliums only under certain cultural conditions. The effect of the organism is the production of granulomatous lesions which grossly resemble those of tuberculosis. There is little known of the early stage of the clinical course because the diagnosis is rarely made until the meningitis is well established. The respiratory tract is the portal of entry, but the interval that precedes the onset of cerebral involvement is unknown. Signs and symptoms of increased intracranial pressure become progressively more severe, and death usually results from respiratory failure. Spread of the disease is by embolic dissemination, and organisms may be cultivated from the blood, urine and spinal fluid. Examination of the spinal fluid is of the greatest help in the diagnosis. The pressure is increased, and the fluid is turbid or gelatinous, with marked increase in proteins. The cell count is elevated, with lymphocytes predominating. The most definite diagnostic procedure is said to be biopsy of the meninges. All treatment has been ineffective except for the use of repeated lumbar punctures.

The authors present the eighth reported case of torula meningitis in association with Hodgkin's disease. The course was insidious and intermittent, but was progressive and terminated fatally. The increasing intracranial involvement caused

severe headaches, visual, sensory and motor disturbances, projectile vomiting, disorientation, coma and respiratory failure. Of interest in the authors' case was the reduction of cells in the spinal fluid after roentgen treatment to the head.

BECK, Buffalo.

OBSERVATIONS AND SURGICAL ASPECTS OF THE CAROTID SINUS REFLEX IN MAN.
BRONSON S. RAY and HAROLD J. STEWART, *Surgery* 11:915, 1942.

This study is based on 13 cases in each of which there was opportunity to observe various aspects of the function of the carotid sinus. In 4 patients a hypersensitive sinus was denervated. A fifth patient showed no changes in pulse or blood pressure with his syncopal attacks (cerebral type) but was relieved of his symptoms after removal of nearby tuberculous lymph nodes. A sixth patient, a woman of 61, had an intracranial arteriovenous aneurysm. Pressure on one carotid sinus produced syncope after the nerves leading away from the sinus had been anesthetized with procaine. Syncope may result from arterial occlusion without participation of the carotid sinus mechanism. Two young patients with presumably normal sinuses were studied in the course of ligation for intracranial vascular anomalies. Five patients with section of the glossopharyngeal nerve provided evidence that afferent impulses from the carotid sinus do not always pass over this nerve alone.

The authors recommend routine preoperative examination of the carotid sinuses. Ether anesthesia does not always obliterate a hypersensitive sinus reflex, and unilateral infiltration of the sinus nerves with procaine is advocated when necessary.

DRAYER, Philadelphia.

Diseases of the Spinal Cord

AN ANALYSIS OF FORTY-NINE CASES OF ACUTE ANTERIOR POLIOMYELITIS.
G. BRUCE LEMMON JR., *Pennsylvania M. J.* 45:1039, 1942.

The cases reported by Lemmon were observed during the epidemic of 1941. All the patients were hospitalized, but it is pointed out that in the presence of an epidemic persons with suspected as well as obvious cases of the disease are usually sent to a hospital. Hence the group is regarded as being fairly representative of the epidemic as a whole.

The course of the disease differed in two important respects from that usually observed in epidemics. 1. Whereas paralysis has been reported to occur in 25 to 35 per cent of patients as a rule, only 27 per cent of the present series showed complete freedom from paralysis. 2. Signs of bulbar involvement were uncommonly frequent, the incidence being 34 per cent as compared with the usual incidence of between 6 to 26 per cent.

DRAYER, Philadelphia.

INJURIES OF THE INTRAVERTEBRAL DISK IN MILITARY SERVICE. J. GRAFTON LOVE, *War Med.* 2:403, 1942.

Love has studied 1,500 cases of protrusion of an intravertebral disk. He finds the results of operative therapy excellent and the mortality less than 0.25 per cent. An intravertebral disk usually protrudes when a person whose back is in flexion receives some unusual stress or strain to the back, such as a sudden fall while in a sitting position. Such an accident causes a protrusion of one of the lumbar disks, most commonly that between the fourth and the fifth lumbar vertebra. The symptoms are pain in the lower part of the back, unilateral sciatic pain and hyperesthesia over the foot on the involved side. The patient walks with a limp; his trunk is bent away from the painful side; there are loss of lumbar lordosis and spasticity of the erector spine muscle; the motions of the spine are limited; hyperextension is painful, and a positive leg-raising sign is present. There is occasionally some loss of sensation over the lateral side of the calf or the lateral and dorsal portion of the foot. The achilles reflex is

diminished or absent. The total protein of the cerebrospinal fluid is more than 40 mg. per hundred cubic centimeters in two thirds of the cases. The diagnosis is confirmed by contrast radiologic studies, with use either of air or of an opaque oil.

The treatment should be expectant for two or three weeks, followed by removal of the disk by laminectomy or resection of the ligamentum flavum.

Love advises as a prophylactic measure that paratroopers, dive bomber pilots, pilots who are catapulted from a ship, pilots who land on a carrier, tank drivers and cavalymen be given a snugly fitting sacroiliac belt or a canvas corset.

PEARSON, Philadelphia.

Peripheral and Cranial Nerves

THE SYSTEMIC NERVOUS AFFINITY OF TRIORTHOCRESYL PHOSPHATE (JAMAICA GINGER PALSY). CHARLES D. ARING, *Brain* 65:34, 1942.

The clinical picture of triorthocresyl phosphate (jamaica ginger) poisoning is well known. Cramps, nausea and vomiting develop immediately after ingestion of the poison. Diarrhea may last several days. Neurologic symptoms develop in from seven to fourteen days. There are cramping, burning and stinging pain in the calves, followed by numbness and tingling. Later there is weakness of the peroneal muscles. About one week after the legs are involved, the hands become weak. Muscle weakness becomes progressively more severe for about a month, when it is usually extensive and pronounced.

Examination reveals inconstant sensory changes. In some cases mild impairment of pain, temperature and touch sense is observed. Vibratory sensation is also occasionally disturbed. Some patients have tenderness of nerve trunks with hyperesthesia. The hands and feet are almost invariably cold, moist and cyanotic.

The tendon reflexes are normally active except that the patellar and arm reflexes are occasionally hyperactive and the ankle jerks are always absent. The presence of active knee jerks and the appearance of involuntary flexor spasms of the legs in many cases suggest involvement of the pyramidal tract, in addition to the obvious disease of the anterior horn cells.

Pathologic study reveals spotty loss of muscle fibers and replacement by connective tissue and fat. The small arterics, capillaries and precapillaries of muscle are involved in a process which, by thickening of all the coats of the vessels, produces an extremely narrow lumen. In some degenerated areas the blood vessels are angiomatous, suggesting new vessel formation. Similar vascular changes are to be observed in many of the abdominal viscera, as well as in the somatic musculature.

All peripheral nerves and roots show severe degeneration of myelin, and there is, in addition, heavy overgrowth of connective tissue.

In the spinal cord, the leptomeninges are thickened. Degeneration of the white matter is invariably observed, and the lateral pyramidal tracts are always involved, especially in the lower segments of the cord. There is also rim degeneration, similar to that often seen in subacute combined degeneration.

In the gray matter of the anterior horns, severe reduction in cells is observed, and the remaining cells show considerable degeneration. Minor degrees of neuronal change only are observed in the brain stem and the cerebrum.

Aring concludes that the disease is essentially a hyperplastic fibrosis of smaller arterioles and capillaries and suggests that the degeneration of the nervous system may be secondary to this vascular disturbance.

MASLAND, Philadelphia.

VESTIBULAR FUNCTIONS IN THE GUILLAIN-BARRÉ SYNDROME. J. HELSMOORTEL and G. MYLE, *Confinia neurol.* 4:148, 1942.

Helsmoortel and Myle describe a mesencephalic or mesencephalospinal form of the Guillain-Barré syndrome with manifestations of involvement of the cochlear

and vestibular nerves. The predominant symptoms were vertigo and ataxia. Caloric, rotating chair and galvanic tests showed evidences of vestibular dissociation. The authors believe that central as well as peripheral lesions may exist in the Guillain-Barré syndrome.

DeJong, Ann Arbor, Mich.

OPTIC NEURITIS FOLLOWING WEIL'S DISEASE.. PETER OLAF PENSKY, *Deutsche Ztschr. f. Nervenhe.* **152**:153 (May) 1941.

Pensky reports the case of a 32 year old man in whom optic neuritis developed two months after the onset of an attack of Weil's disease. Visual loss was first noted about twenty days after recovery from the acute infection.

The neuritis could be observed only in the right eye because of old tuberculous keratitis in the left. In the right eye visual acuity was slightly reduced, and there was 0.75 diopter of swelling of the disk. There were no other neurologic symptoms or signs. The swelling of the disk gradually subsided, and vision returned to normal in the course of the next four months.

The author comments on the rarity of optic neuritis during the course of or following Weil's disease. The 6 cases previously reported in the literature are briefly reviewed. He believes that the spirochete of Weil's disease has an affinity for the nervous system but that in most instances this is manifested by meningeal or polyneuritic symptoms.

Merritt, Boston.

Treatment, Neurosurgery

THE MANAGEMENT OF NEUROSYPHILIS. BERNARD DATTNER and EVAN W. THOMAS, *Am. J. Syph., Gonor. & Ven. Dis.* **26**:21 (Jan.) 1942.

Patients with neurosyphilis often present individual problems, and no generalization will cover the complete management of every case. However, the authors review their experiences and those of others in an attempt to evaluate those factors which constitute active neurosyphilis.

Many physicians and clinics still depend on incomplete reports on the spinal fluid and clinical signs and symptoms. Some patients are referred to a hospital for fever therapy merely because of a positive Wassermann reaction of the spinal fluid, while others are referred only after clinical manifestations have become well established. There is a general tendency to evaluate results chiefly in terms of clinical improvement. This may be inaccurate because such evaluation is frequently difficult to determine. The criterion is not always a satisfactory guide to management in that it suggests little about the permanent effects of treatment. The authors emphasize that it is of greater value to determine the activity of the pathologic process in the light of the necessary treatment rather than to attempt accurate differentiations of neurosyphilis.

The first task in the management of neurosyphilis is to ascertain the activity within the central nervous system. One guide is the appearance of new clinical symptoms, but the authors point out that (1) signs and symptoms may persist as a result of past activity and are not proof of a continuing active process, (2) improvement in clinical symptoms may only be transitory and (3) the syphilitic infection may be very active within the central nervous system and still be asymptomatic.

The second guide concerning activity of the syphilitic process is examination of the spinal fluid. The authors make the following generalizations: 1. A positive Wassermann reaction of the spinal fluid alone is not proof of an active syphilitic process but merely an indication of the specific nature of the infection. The cell count and globulin and total protein values are the best indicators of activity. 2. Reactions of the spinal fluid may vacillate during the first five years of a syphilitic infection. 3. After infection of five years' duration a negative reaction of the spinal fluid will not become positive. 4. It does not follow that a completely negative reaction of the spinal fluid always indicates inactivity within the central nervous system. Vascular syphilis and tabes dorsalis may be associated with such a reaction. The latter process, however, is one which continues to

produce symptoms long after the active infection may have disappeared. 5. An actively positive reaction of the spinal fluid with an increase in cells and protein five years after the initial infection is a danger signal. 6. In treated patients the Wassermann and colloidal gold reactions of the spinal fluid may remain positive after treatment has successfully checked the process. If the cell count and the protein value show improvement, it is unlikely that syphilis will again become active in the central nervous system. 7. It is possible to inhibit the signs of activity in the spinal fluid without permanently checking the activity in the central nervous system.

The aim of treatment is to achieve optimum results in the shortest period without injury to the patient. Experience of investigators all over the world indicates that a combination of chemotherapy and induction of fever is the most effective treatment of all forms of neurosyphilis. Tertian malaria is believed to be the method of choice in induction of fever. After fever therapy the question arises as to how and what type of chemotherapy should follow. There is no unanimity of opinion on this subject. The controversy of pentavalent versus trivalent arsenicals is still in question.

The authors have evolved their plan of treatment following fever; they give daily injections of 0.06 Gm. of mapharsen immediately after the last fever treatment, with reexamination of the spinal fluid in six months. When weekly treatments are given, a six month course is advised. The spinal fluid is checked for activity in six months. The authors believe their intensive method of treatment is safe and that it is not necessary to continue chemotherapy for years.

BECK, Buffalo.

COMBINED ARTIFICIAL FEVER, CHEMOTHERAPY, AND VACCINOTHERAPY IN THE TREATMENT OF NEUROSYPHILIS. ALBÉRIC MARINE, *Am. J. Syph., Gonorr. & Ven. Dis.* 26:234 (March) 1942.

Marine reviews three and one-half years' experience in the treatment of the various types of neurosyphilis with combined artificial fever and chemotherapy, with particular reference to the utilization of vaccine as an adjunct in the production of fever. The method of treatment was as follows: At 7 a. m. the patient received an injection of an arsenical drug and was immediately given five hours of artificial fever at 105 F. On the third and fifth days he was given an injection of a fever-producing vaccine and a bismuth compound. This procedure was carried on for ten weeks, during which a total of fifty hours of fever at 105 F., ten injections of an arsenical drug and twenty injections each of vaccine and of a bismuth compound were given. Treatment was then carried on in the outpatient department with an arsenical and a bismuth compound. Lumbar puncture was performed before and after the series of treatments.

The combined heat-drug-vaccine therapy was not found to be debilitating, since emaciated patients gained weight. Lightning pains diminished or disappeared, and tension states decreased. Not a single death occurred among the 265 patients treated.

The author believes that favorable serologic results have occurred in a large percentage of patients. A real advantage claimed for artificial fever over malaria therapy is that a second course of fever treatments can easily be given.

BECK, Buffalo.

SOME NEW APPLICATIONS OF SYNTHETIC VITAMIN E THERAPY. GEORGE A. BLAKESLEE, *J. Nerv. & Ment. Dis.* 96:184 (Aug.) 1942.

Blakeslee reports the results of vitamin E therapy in 3 cases of peripheral neuritis with the Guillain-Barré syndrome, 1 case of amyotonia congenita and 1 case in which the differential diagnosis between amyotrophic lateral sclerosis and muscular dystrophy was uncertain. Alpha tocopherol acetate, 30 mg. a day, was given to each patient; it was thought that there was definite improvement in all cases.

CHODOFF, Langley Field, Va.

REPORTS OF PARTIAL FRONTAL LOBECTOMY AND FRONTAL LOBOTOMY PERFORMED ON THREE PATIENTS. W. J. MIXTER, K. J. TILLOTSON and W. WIES, *Psychosom. Med.* 3:26 (Jan.) 1941.

Mixter, Tillotson and Wies report the effects of partial bilateral frontal lobectomy in a 17 year old youth who had been subject to frequent convulsive seizures since childhood, with evidence of mental deterioration. Atrophy and adhesions were evident in the portions of the brain removed. Operation resulted in a decided reduction in the frequency of the convulsive seizures and apparently in some improvement in conduct and behavior. Bilateral lobotomy was performed in cases of agitated depression occurring in men aged 58 and 62. The authors verified the observations of Freeman and Watts that immediate relief from anxiety and nervous tension followed the operation. Among the psychotic manifestations favorably influenced were negativism, perseveration, extreme agitation and mannerisms. Ideas and emotions which prior to operation produced gross psychotic behavior did not seem to be highly charged with affect after operation. Loss of spontaneity, initiative and interest and some impairment of recent memory with relative lack of concern about the future are the noteworthy destructive effects of prefrontal lobotomy. Nevertheless, the emotional responses are adequate to deal with external situations. The authors conservatively conclude that, in view of the definite danger attendant on operation, prefrontal lobotomy should be limited to patients who appear to be completely and permanently disabled by their psychiatric disorder.

SCHLEZINGER, Philadelphia.

Muscular System

GOITER WITH ASSOCIATED MYASTHENIA GRAVIS. GEORGE F. KOWALLIS, SAMUEL F. HAINES and JOHN DEJ. PEMBERTON, *Arch. Int. Med.* 69:51 (Jan.) 1942.

Since 1908 10 cases have been noted in the literature in which exophthalmic goiter was associated with myasthenia gravis. The authors report 3 cases of exophthalmic goiter and 1 case of adenomatous goiter and hyperthyroidism associated with myasthenia gravis. In 1 case a subtotal thyroidectomy was performed, with alleviation of symptoms of both processes.

Exophthalmic goiter and myasthenia gravis have certain common characteristics. Both occur at any decade of life, and females are more frequently affected than males. Muscular weakness is common to both, as are spontaneous exacerbation and remission with a tendency to progression. But in myasthenia gravis ptosis of the upper lid is usual, while in exophthalmic goiter the lids are usually retracted. Enlargement of the thymus is not a differential factor. A clinical response to prostigmine is characteristic of myasthenia gravis, while for exophthalmic goiter iodine is more or less specific. This is of no diagnostic help if myasthenia gravis occurs in association with hyperthyroidism. The basal metabolic rate is unchanged in cases of uncomplicated myasthenia gravis.

Pathologic studies were made in 99 cases of myasthenia gravis, and in 45 of the cases prominent anatomic lesions of the thymus body were present. In contrast, in 74 fatal cases of exophthalmic goiter the thymus gland was hypertrophic. In a small series of treated patients with exophthalmic goiter who died of causes unrelated to the goiter, there was no instance of hypertrophy of the thymus gland. For adequately treated exophthalmic goiter the prognosis is good, but for myasthenia gravis the outlook is grave. It is especially poor if the diseases coexist, but even then remissions are known to occur.

Surgical treatment of exophthalmic goiter complicated by myasthenia gravis is difficult because it is important that the patient be able to cough and swallow to dispose of tracheal mucus, which is common after thyroidectomy. In the authors' surgical cases, prostigmine was used; the resulting muscular improvement was such that no complications were encountered.

BECK, Buffalo.

Muscular System

MUSCLE CHANGES IN MYOPATHIES AND DYSTROPHIA MYOTONICA. JULIO ARANOVICH and ALFREDO C. MENZANI, *Rev. neurol. de Buenos Aires* 7:147 (April-June) 1942.

Biopsies of muscle in 3 cases of progressive muscular dystrophy and 6 cases of dystrophia myotonica were studied by Horteaga's technic. In the cases of progressive muscular dystrophy the authors found hypertrophied fibers, collagenous proliferation, atrophy of the sarcolemma and slight nuclear increase. They distinguish three stages of the atrophic process. In 3 cases of dystrophia myotonica they observed no lesion of the muscular fibers, connective tissue or blood vessels and only increase of nuclei; in the other 3 cases there were atrophy and sinuosity of the muscular fibers, disappearance of the crossed and longitudinal striations, a great quantity of peripheral and axial nuclei and proliferation of the connective tissue and, in 1 case, of the vascular tunics.

BAILEY, Chicago.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

ROY R. GRINKER, M.D., *President, in the Chair*

Regular Meeting, May 14, 1942

Afferent Trigeminal Pathways as Determined by Evoked Potentials.

DR. H. W. MAGOUN and MR. W. A. MCKINLEY.

With oscillographic recording of potentials evoked by stimulation of peripheral nerves, the central course of fast conducting afferent trigeminal fibers has been studied in the cat. In their course in the sensory root and the spinal fifth tract, fibers of the three divisions of the trigeminal nerve are laminated in a dorsoventral order, which is the inverse of their distribution in the face. Primary fibers of the mandibular division are detected as far caudally as the obex, and those of the maxillary and ophthalmic divisions, as far caudally as the first cervical segment.

The neurons of the nucleus of the spinal fifth tract fired by primary fibers are laminated in a dorsoventral order, similar to that of the tract, but with greater overlap. No rostrocaudal projection on the secondary neurons could be detected, however, for secondary spikes were recorded throughout the extent of the nucleus of the spinal fifth tract in the case of each trigeminal division.

Secondary trigeminal pathways pass diffusely across the reticular formation to the ventromedial part of the opposite side of the medulla and ascend in and adjacent to the medial lemniscus, in relation to similar fast conducting pathways from the limbs. These connections terminate in the ventral thalamic nucleus: the limb pathways in its posterolateral, or external, division and the trigeminal pathways in its posteromedial, or arcuate, division.

The discharge of these pathways fires cells of the ventral thalamic nucleus, the axons of which pass forward in the internal capsule toward the cortex. Apparently, by some relay system the centrum medianum is also fired, but considerably later. No evoked potentials were detected in other thalamic nuclei.

DISCUSSION

DR. A. EARL WALKER: Through such a contribution to neuroanatomy as has been heard tonight the neural pathways within the brain stem are beginning to be understood. Not many years ago the secondary trigeminal pathways were considered to lie near the posterior longitudinal bundle, as postulated by Wallenberg and van Gehuchten. The true position of these tracts has been demonstrated only recently. Marchi studies of the secondary pain pathways suggest that there is a second topical arrangement of the fibers in the mesencephalon. Dr. Magoun has mentioned the mediolateral arrangement of fibers, those from the face being medial and those from the lower extremity lying on the periphery. A certain dorsoventral lamination is also present, so that the fibers from the lower extremity lie dorsal to those from the upper extremity, both of which are dorsal to those from the face.

The topical arrangement of the fibers terminating in the thalamus as determined by Dr. Magoun's experiments is in full accord with the results of previous studies and requires no further comment.

DR. PERCIVAL BAILEY: I did not understand how Dr. Magoun tested the "onion skin" hypothesis, and I wish he would go into the details. As I under-

stand it, the peripheral layer of "onion skin" is supposed to descend farther in the bulb than the central layer.

DR. H. W. MAGOUN: Mr. McKinley and I have not explored the possibility of afferent connections to the corpus striatum. On a few occasions face and limb potentials have been recorded from the subthalamus and the zona incerta; these may indicate the presence of an extrathalamic collateral from the lemniscal pathway.

With reference to the similarity of potentials from the main sensory and the spinal fifth nucleus and the caudal extent of connections in the spinal fifth tract, it may be emphasized that potentials were recorded only from fast-conducting and presumably large trigeminal fibers, which Harrison and Corbin (*Anat. Rec.* 82:26, 1942) have shown to be concerned with tactile sensibility. It would appear that touch is mediated not only by main sensory but to a considerable extent by spinal fifth nerve connections.

The "onion peel" theory was examined by comparing the results of stimulating the anterior mental and auriculotemporal nerves. Since the areas innervated by these nerves are located at the center and periphery of the "onion," a significant difference in the distribution of their central connections might be expected. They were found, however, to be identical.

Myasthenia Gravis: Treatment and Relation to the Thymus. DR. L. M. EATON, Rochester, Minn.

The prostigmine test advocated by Viets and Schwab has been found a most important aid in the diagnosis of myasthenia gravis. This test, however, may not be conclusive, particularly in cases of the milder form. In such cases the quinine test, introduced by Harvey and Whitehill, is of value. Quinine greatly intensifies the symptoms of myasthenia gravis. Objective evidence of myasthenia gravis can be obtained in cases of the milder type by administering quinine and prostigmine to the patient without the patient's knowing the name of the drug and observing the weakening effects of quinine and the strengthening effects of prostigmine.

Prostigmine bromide, administered orally, is the basic treatment for the average patient. Doses of 15 to 30 mg. are repeated as often as necessary to maintain a satisfactory degree of strength. Trial periods during which guanidine hydrochloride, ephedrine or potassium chloride is combined with prostigmine are necessary to determine the most beneficial regimen. If these adjuvants allow a significant reduction in the amount of prostigmine required or sufficiently increase the patient's feeling of well-being, their use are continued. Quinine, thyroid and procaine hydrochloride should be used cautiously in cases of myasthenia gravis, since these agents may intensify the symptoms.

The relation of myasthenia gravis to the endocrine system, particularly the thymus gland, has been under consideration. The presence of thymic abnormalities in approximately half the cases in which death was caused by myasthenia gravis and the experiences with surgical removal and roentgen irradiation of the thymus furnish unequivocal evidence of the relation between myasthenia gravis and the thymus gland. The value of extirpation and irradiation of the thymus gland in the treatment of myasthenia gravis is not established, but the results are encouraging and warrant further study. The effect of pregnancy on the course of the disease is striking but not uniform. The frequency with which exophthalmic goiter and myasthenia gravis are associated furnishes additional evidence of the relationship of myasthenia gravis to endocrine disturbances.

Roentgenograms of the thorax, including lateral views to rule out enlargement of the thymus, should be made in all cases of myasthenia gravis. If an enlarged thymus is detected, roentgen irradiation, surgical removal or both methods of treatment are indicated. In the 2 cases of myasthenia gravis in which thymic tumors were removed at the Mayo Clinic, remissions of the myasthenia began within two months after irradiation of the region of the thymus. The observation lends weight to the clinical impression that the mediastinal tumor

was a factor in the production of the patient's symptoms. In the present state of knowledge, roentgen irradiation of the thymus is worth trying, even though roentgenographic evidence does not indicate thymic enlargement. Every patient who has myasthenia gravis should be studied for evidence of exophthalmic goiter and vice versa.

DISCUSSION

DR. VICTOR E. GONDA: I should like to ask the author two questions: First, did he observe in these cases the cessation of the knee jerk or any other reflex after repeated elicitation? Second, did he obtain the so-called myasthenic reaction of Jolly?

I should mention the only miracle that I have observed in connection with myasthenia gravis. In 1925 Dr. Bassoe and I made a diagnosis of myasthenia gravis in a woman, who subsequently underwent a series of treatments with tryparsamide and recovered. She has been a hard-working woman ever since, without the slightest manifestation of myasthenia.

DR. ROY R. GRINKER: One of my most embarrassing moments concerns a patient with myasthenia gravis in whom the first symptoms developed during the early months of pregnancy. I urged strongly that the pregnancy be terminated, but she insisted on going through with it; she subsequently improved and was better than ever before. Since delivery she has had relapses, which have been successfully treated with ephedrine and prostigmine.

I should like to ask about mediastinal tumors other than those of the thymus, and inquire how Dr. Eaton fits them into the theory of the origin of myasthenia gravis; we have seen such tumors. Another phenomenon for which I have seen no explanation is the frequent accumulations of round cells in the muscles. These lymphorrhagias have also been reported in certain cases of hyperthyroidism. What does Dr. Eaton think is the significance of these infiltrations in cases of myasthenia gravis?

DR. A. J. ARIEFF: There have been many cases in which the use of prostigmine was effective, but the after-effect left the patient in a more myasthenic condition than prior to the use of the drug. I have 1 such case. The patient does well only on combinations of physostigmine, ephedrine and prostigmine. I have had her under treatment with each of the drugs alone and with all three of them together, and it is only by the latter method that she gets along. The results were controlled by dynamometric studies.

DR. R. P. MACKAY: May I ask Dr. Eaton what is the longest remission he has observed in a case of myasthenia gravis? A young man came to me four or five years ago with the disease, and he was relieved by prostigmine. After a few weeks he was able to discontinue the drug and has been well since. He married against my advice in the interim. Incidentally, he was not given tryparsamide.

DR. LEE M. EATON: Dr. Gonda asked whether loss of the knee jerk has been noted after repeated testing. I have not observed this, and I have made such tests frequently. Neither have I observed fatiguing of the pupillary light reflex to repeated flashes of light. The pupils of the patient presented in the motion picture reacted sluggishly at the height of the disease, but with normal rapidity after remission of the myasthenic symptoms.

Remissions of varying duration occur spontaneously in myasthenia gravis. I recently saw a young man profoundly weakened who had acute attacks on an average of once a year. They were always of short duration, lasting only two or three weeks; between attacks he was entirely well. His response to prostigmine was such as to leave no doubt as to the correctness of the diagnosis. Spontaneous remissions of a year or more are common, and remissions of nine years' duration have been reported. Since such spontaneous remissions do occur, it is unwise to draw conclusions from 1 or 2 cases in which remissions seem to follow a specific therapeutic procedure. The results of the removal of thymic tumor in cases of this disease must not be judged until many more cases have been studied.

Dr. Grinker has asked concerning the association of myasthenia gravis with mediastinal tumors other than those originating in the thymus. Thymic tumors vary so much in location and roentgenographic appearance that I do not believe it can be stated after clinical examination alone that any intrathoracic tumor associated with myasthenia gravis is not of thymic origin. In necropsies at the Mayo Clinic the only intrathoracic growth encountered has been tumor of the thymus. I have had 2 cases of great interest. In 1 case the diagnosis of malignant growth of the pleura and pericardium was made. Pleural and pericardial effusion had occurred on two occasions. The condition responded to roentgen irradiation, and the myasthenic symptoms disappeared. In retrospect, I believe the tumor must have originated from the thymus. In another case a widened mediastinal shadow was found on roentgenologic examination. This shrank rapidly after irradiation. The tumor was thought to have been a lymphoma. This patient subsequently died in a veterans' hospital, and I am awaiting a report of the postmortem study.

I do not know of any adequate explanation for the lymphorrhagias observed in the muscles in cases of myasthenia gravis. Weigert, mistakenly, looked on them as metastatic lesions from a sarcoma of the thymus. Others have stated that they represented an infectious process. They may be seen in muscles not involved clinically and are sometimes not found in muscles which are weakened.

Patients sometimes complain that they feel weaker after the effects of prostigmine have worn off than they would if none had been taken. I do not know the explanation of this. In such cases, ephedrine and guanidine hydrochloride may lessen the "let-down" which follows cessation of the effect of the prostigmine.

An extract of the thymic tumors removed surgically has not been injected into the patients at the clinic. In the first case two extracts were prepared, one in water and one in alcohol. The results of injection of these extracts into rats were inconclusive. The cystic fluid removed in the second case has been frozen, and it will be tested later.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

JOHN M. DORSEY, M.D., *President, in the Chair*

Regular Meeting, Sept. 17, 1942

Clinical Evaluation of the Mosaic Test. DR. BERNARD L. DIAMOND and DR. HERBERT T. SCHMALE, Ann Arbor, Mich.

A modification of Lowenfeld's mosaic test was given to over 200 selected patients. Color photographs were taken of the designs executed, and these have been kept to form a permanent file for interpretation and comparison. It is believed that the mosaic performance should be regarded as an integrated whole and evaluated as an entity. The test is graded on the basis of achievement of a satisfactory and well organized *Gestalt*. There are indications that the abnormalities in the mosaic pattern appear early and are little affected by significant changes in attitude, affectual states and social adjustment. Important differences were noted between the color responses of schizophrenic subjects and those of patients with organic and affective disorders. Specific diagnostic interpretation, particularly with reference to schizophrenia, was possible with a reasonable degree of statistical validity. Although its interpretation requires experience, the simplicity and ease of administration of the mosaic test should give it a definite place in the examination of the neuropsychiatric patient.

Psychiatry and Morals. DR. RICHARD L. JENKINS, Ann Arbor, Mich.

This article will be published in *Mental Hygiene*.

PHILADELPHIA NEUROLOGICAL SOCIETY

F. H. LEWEY, M.D., *Presiding**Regular Meeting, May 22, 1942***Tumor of the Cauda Equina with Unusual Onset and Symptoms: Report of a Case. DR. FRANCIS C. GRANT and DR. EVERETT O. JEFFREYS.**

G. L., a bulldozer operator aged 41, who had previously been well, was returning home on the night of Dec. 26, 1941, when he suddenly sneezed violently. He immediately experienced severe pain in the lower part of the back and a sensation of "pins and needles shooting up and down his spine." The pain soon came to radiate into both lower extremities. The severity and persistence of the pain prompted him to consult a physician, who applied adhesive strapping and told the patient that it was a sprain.

He was unable to sleep because of the ever increasing pain. The following morning he attempted to arise, but the lower extremities collapsed beneath him and were so weak that he was unable to walk. There was also pronounced hesitancy in urination. Within thirty-six hours after the onset he was unable to void even with effort. No sensory phenomena other than pain, no paresthesias and no inability to differentiate touch, temperature or pain sensation was experienced. The patient entered the Graduate Hospital on December 31, four days after the onset, completely paralyzed in both legs and writhing in pain.

The signs of involvement at that time were: (1) complete flaccid paralysis of both lower extremities; (2) greatly diminished reflexes of both lower extremities, including the balanoanal and cremaster reflexes; (3) painful distention of the bladder up to the umbilicus; (4) appreciation throughout of all modalities of sensation and no saddle hypesthesia; (5) positive Naffziger sign; (6) bilateral Lasègue sign; (7) hypertonic rectal sphincter; (8) absence of fever and leukocytosis; (9) negative Wassermann reaction; (10) absence of roentgenographic evidence of involvement of the lumbodorsal and sacral portions of the spine; (11) an initial pressure of 400 mm. (water pressure) and dark, xanthochromic, old sanguineous fluid obtained on lumbar puncture, the puncture precipitating such exacerbation of pain in the genital region that a Queckenstedt test could not be performed, and (12) complete subarachnoid block revealed by injection of 3 cc. of iodized poppyseed oil, with the lower level at the lower border of the second lumbar vertebra.

Removal of the first, second and third lumbar laminae gave adequate exposure of the lesion. A large tumor of the cauda equina was observed encircling the conus medullaris with hemorrhage below the tumor into the caudal sac. Large venous varices entered both poles of the tumor, and the filum terminale was incorporated in the tumor and had to be sacrificed in the complete removal of the growth. The roots of the cauda equina were entwined in the blood and fibrinous mesh. The tumor was removed in its entirety. The postoperative course was uneventful, and recovery was rapid. Bladder function was normal by the ninth postoperative day. The patient was able to walk unaided on the twenty-sixth postoperative day and is now back at his former occupation, without any appreciable residual signs.

Dr. Lewey reported that the tumor was very vascular and definitely malignant, but that it could not be classified with absolute certainty. However, it resembled a hemangioblastoma.

DISCUSSION

DR. FRANCIS C. GRANT: I was much interested in this man when he was admitted because of the abrupt onset of his symptoms with pain. I suspected that he might have an epidural abscess. Dr. Jeffreys was alert enough to realize that possibility and made a lumbar puncture. This test eliminated the possibility of

an abscess. We both concluded that the patient had a lesion of the cauda equina. He was operated on, with the results stated.

I am not entirely surprised that one should have bizarre neurologic signs with a tumor of the cauda equina. Since the roots can slip from side to side under a tumor, the development of symptoms may be unexpected. It is impossible to be dogmatic about the symptoms or the sequence of their appearance with tumors in this area. There is not necessarily any loss of sphincter control. The clinical picture that appears in cases of tumor of the cauda equina depends on the acuteness of the onset and the degree to which the roots are compressed.

I had the privilege the other day of operating on a patient of Dr. Winkleman's who without question had had a tumor of the cauda equina for twenty-one years. For ten years roentgenographic evidence was positive for a lesion in that area; yet the man was able to go about and symptoms in his lower legs developed only gradually. I found an ependymoma of the cauda equina.

DR. A. GORDON: It is interesting to hear Dr. Grant say that one cannot always rely on the classic symptoms for diagnostic purposes. Time and again my associates and I have encountered cases of tumor of the spinal cord, not exactly of the cauda equina, in which the acute symptom—that of pain—should have been expected and there was no pain whatever during the entire course of the disease. We have seen cases of other pathologic conditions producing pressure, such as deformity of the spinal canal or osseous lesions pressing directly on the cord, in which pain should have been expected but did not occur. The reason is simply that we are not absolutely accurate and perfect in our diagnostic work.

May I ask Dr. Grant whether there were any objective sensory disturbances, such as analgesia? Was there any involvement of the sphincters? As I understand, the tumor was in the upper part of the cauda equina. A tumor in that position produces direct pressure on the conus. If there was no sphincter trouble or objective sensory disturbance the case was really unusual.

There are supposedly no irregular cases, as Dr. Grant said, but it must be admitted that for surgical or medical diagnosis, one must follow the whole course of the disease and examine the status of the sensory symptoms from day to day. Only in that way can one make the correct diagnosis in so-called unusual cases.

DR. EVERETT O. JEFFREYS: This tumor was a high-placed lesion of the cauda equina encircling the conus medullaris. It involved the filum terminale, the sheath of the latter seeming to form the capsule, or envelope, of the tumor. Over the capsule was the venous rete, or varices, extending well up over the conus and the lower portion of the spinal cord.

I am not sure whether I made adequate mention of the sphincters in this case. The patient had no loss of sphincter control, but had hypertonicity of the rectal sphincter and presumably of the urethral sphincter, in that he was unable to void and the bladder was distended to the level of the umbilicus without any overflow. These symptoms had subsided by the ninth postoperative day.

DR. A. GORDON: What was the sensory state of the perineum?

DR. EVERETT O. JEFFREYS: This man had no sensory changes referable to the lower extremities or to the perineum. There was no dissociation anesthesia, which is so frequently emphasized with lesions of the cauda equina. Most of the leading neurology textbooks, such as those of Purves-Stewart, Bing and Haymaker and Brain, stress the constancy of the perineal dissociation anesthesia with tumors of the cauda equina.

There was not even hyperalgesia, as one might expect with hemorrhage around the roots of the cauda. The absence of sensory phenomena in the saddle area and in the extremities and the sudden and peculiar mode of onset of symptoms with a lesion of this size impress me as unusual. I believe that it is a well accepted fact that in cases of lesions involving both the cauda equina and the conus medullaris, the symptoms referable to the cauda equina mask those of the conus.

Electrophoretic Study of Concentrated Cerebrospinal Fluid. DR. ELVIN A. KABAT, DR. DAN H. MOORE and DR. HAROLD LANDOW, New York.

Specimens of cerebrospinal fluid of normal and of elevated total protein content obtained from patients with neurologic disorders were concentrated to small volume by dialysis in the cold under pressure and studied in the Tiselius micro-electrophoresis apparatus, a cell of about 2 cc. capacity being used.

The electrophoretic patterns were similar to those of the plasma proteins. In cases in which the total protein content of the spinal fluid was elevated, all of the plasma proteins were present; in those in which the protein levels were normal, alpha globulin and fibrinogen were frequently not detected. When the total protein of the fluid was increased, the greater part of this increase was generally due to albumin. Alterations in the pattern of the serum proteins were reflected in the cerebrospinal fluid. Patients with lymphogranuloma venereum, who showed a high level of gamma globulin in the serum, had a high gamma component in the spinal fluid. The albumin: globulin ratio, however, was not so low in the spinal fluid as in the blood of these patients.

A spinal fluid with an abnormal colloidal gold curve showed a high gamma globulin level, and separation studies indicated that all of the colloidal gold activity is contained in the gamma fraction. The data suggest that spinal fluid protein is derived mainly from the blood but that some synthesis of globulin may take place within the nervous system.

DISCUSSION

DR. L. B. CHAMBERS, Union City, Ind.: This study of electrophoresis had its beginning as far back as 1803 or 1804, in the work of a physicist named Reuss. It is encouraging to know that after one hundred and forty years a technic devised by a physicist has finally come to have its bearings on medicine and biology, fields which at that time were completely foreign to physicists.

Just how far the method can be used in diagnosis and in interpretation of pathologic states of course remains a question. About two years ago Longsworth and McInnes, of the Rockefeller Institute, in discussing electrophoresis of serum and plasma, predicted that in a short time the electrophoretic method would be in as common use in hospital laboratories as is the blood count at present. Their studies indicated that electrophoretic analysis of the albumin-globulin distribution in serum was of particular diagnostic value.

All of course assumed that the sensitivity of the electrophoresis apparatus itself would have to be increased over and above what had been developed by Tiselius and his collaborators in Sweden and by McInnes in New York before the proteins of the spinal fluid could be adequately separated and identified. However, Dr. Kabat is to be congratulated on having introduced a method of negative dialysis which makes possible concentration of the proteins to such an extent that their detection and separation can be accomplished.

The next step, if electrophoresis of the spinal fluid is to be used routinely for diagnosis, probably will lie in improving the speed with which the procedure can be carried out. It takes several days to make a single analysis of this type. In many cases the test would still be worth while, but it would be advantageous to speed the process.

DR. E. A. SPIEGEL: I should like to ask Dr. Kabat for more detail about the interpretation of his observations on permeability of the capillaries to various proteins. If the meshwork of the capillary wall does not allow some large molecules or particles to go through, and if, then, the diameter of that meshwork is increased, one would expect that some of the large particles would be able to pass through. The question depends, of course, on quantitative relationships, and I should appreciate it if Dr. Kabat would give some of the observations on which he bases his conclusions regarding the double origin of the proteins in the spinal fluid.

DR. G. D. GAMMON: I should like to ask what is found in cases of vascular occlusion in the nervous system, cases in which plugging of blood vessels with

destruction of brain tissue has occurred, and whether any changes that appear in the course of virus diseases, such as poliomyelitis and encephalitis, are characteristic of these infections.

DR. F. H. LEWEY: I am sorry not to have invited Carl Lange to this meeting to enjoy the verification of his original theory, namely, that the substance responsible for the initial colloidal gold reaction is a globulin, that its appearance precedes increased permeability of the membranes and that, on the other hand, albumin prevails over globulin once the meninges become permeable.

May I ask Dr. Kabat what minimal amount of spinal fluid is requisite for the cataphoresis and what globulin-albumin mixtures correspond with the usual curves in the colloidal gold reaction?

DR. ELVIN A. KABAT: In reply to the first question, in serum there is usually about 70 per cent albumin and 10 per cent gamma globulin, and no alteration in permeability could explain a spinal fluid with 50 per cent albumin and 50 per cent gamma globulin. Any change in permeability would let proportionately more albumin through, since albumin has a smaller molecule than globulin. While with an increase in permeability more globulin will pass through than with the original permeability, much more albumin will pass through, relatively speaking.

In answer to the second question, we did not have any cases of poliomyelitis and only 1 or 2 cases of encephalitis. In 1 case of encephalitis in which we had a very low protein level of 16 mg. per hundred cubic centimeters we could not find any particular change, but at these low protein concentrations the method is less precise. In 1 case of "meningitis of unknown etiology," with a protein content of 760 mg., all of the components were increased and the albumin level rose to 500 + mg. out of the 760 mg.; so there was a tremendous increase in total albumin in relation to the other components.

It would be of considerable interest to study some of the infectious diseases of the nervous system from the standpoint of the protein ratio of the spinal fluid. However, I think encephalograms are seldom, if ever, performed in cases of such disorders.

The other question was in regard to vascular disturbances. Whenever there is any suspected vascular disease, I am told that one is reluctant to remove any of the spinal fluid.

In answer to Dr. Lewey's question concerning the minimum amount of spinal fluid necessary: One needs 2 cc. of the concentrated fluid for the microelectrophoresis cell. One must also have a minimum concentration of 5 mg. of protein per cubic centimeter. About 10 to 12 mg. of spinal fluid protein is needed for analysis. Now, if the protein level of the spinal fluid is elevated, say, to 10 mg., one conceivably could get along with 10 to 12 cc. of spinal fluid. But if the spinal fluid protein is only 20 mg. per hundred cubic centimeters, one would have to have 50 to 60 cc. of fluid to make an adequate analysis. At this limit of 10 to 12 mg. the error is proportionately greater than it is with more concentrated solutions.

My associates and I like to have about 60 cc. of fluid containing 40 to 50 mg. of protein per hundred cubic centimeters to work with. It is possible to get down to the lower range, and we have done it, but we do not feel that we can get as reliable information.

We usually can get only 60 cc. of spinal fluid in a case in which an encephalogram is made. In cases of disorders of the nervous system, with an elevated protein content of the spinal fluid, one can get sufficient fluid readily by lumbar puncture. The difficulty has been to get what we consider an adequate normal control, and for that we try to get 60 cc. of spinal fluid. I think we did that in a few cases.

With regard to the colloidal gold curve, the gamma globulin itself has all of the colloidal gold activity, and with the pure gamma globulin one would always get a curve characteristic of dementia paralytica.

We have frequently had cases in which the original spinal fluid had a colloidal gold curve of 111122111. That represents a beginning midzone and is usually considered normal. In most cases, if the gamma globulin was separated out, we

got a curve of the dementia paralytica type; again, the problem of having little protein to work with presented a difficulty. As I mentioned, we took a serum with a positive colloidal gold curve, for example, 4433221110; the curve for the separated gamma globulins, then, was something like 5555443211. If we took a sufficiently small amount of the gamma globulin from the serum, say one tenth of the amount present in the serum, and added the original amount of albumin, we could get a colloidal gold curve that was perfectly normal—all zeros. On the other hand, if we added an intermediate amount of albumin, not enough to inhibit completely, we could get back a midzone curve, 1122321110.

I believe, therefore, that the colloidal gold reaction—whether one obtains a curve of the dementia paralytica or the midzone type—is determined chiefly by the ratio of albumin to globulin in the spinal fluid.

Spontaneous Subarachnoid Hemorrhage: An Analysis of Fifty Cases.

DR. B. A. HIRSCHFIELD, Trenton, N. J., DR. A. S. TORNAY and DR. J. C. YASKIN.

Spontaneous subarachnoid hemorrhage should be recognized as a clinical entity for prognostic and therapeutic purposes. The hemorrhage is due to rupture of an aneurysm or an otherwise diseased blood vessel of the circle of Willis or of its extracerebral branches. Many of the aneurysms are congenital, which accounts for the hemorrhage in young persons; a few are mycotic, and many others are atherosclerotic in origin, the last type being frequently associated with hypertensive vascular disease. In our series of 50 cases occurring within the last three years, the group with hypertension constituted a considerable portion (66 per cent).

The clinical course is fairly constant and is characterized by sudden onset with severe headache, nausea, vomiting and clouding of consciousness, followed within a few hours by evidences of meningeal irritation, which is not always pronounced, and by focal cerebral signs, which are inconstant and changeable. The condition is differentiated from other causes of meningeal irritation by the presence of blood in the spinal fluid and the absence of evidences of trauma, infective meningitis and intracerebral disease processes.

The immediate prognosis, on the whole, is much better than for the various forms of intracerebral hemorrhage. However, recurrences are not uncommon.

In the treatment, lumbar puncture is often useful in relief of rapidly increasing intracranial pressure and its symptoms, such as headache. The indications and contraindications of spinal puncture as a therapeutic measure in cases of this condition are discussed.

DISCUSSION

DR. PHILIP Q. ROCHE: When one is determining the relationship of the hazard of bleeding to high blood pressure, at what point is hypertension said to exist? An arbitrary measure of pressure having once been set, does such a standard operate exclusive of other factors in producing bleeding?

DR. A. GORDON: I have seen a number of spontaneous subarachnoid hemorrhages. The most interesting symptom to remain fixed in my memory—so much so that in every case which came under my observation I have looked for it and found it—is somnolence. I recall distinctly the case of a physician who was referred to me by the late Dr. J. DaCosta, with the following history: The physician would sit in his office, see his patients and fall asleep; he would be awakened and fall asleep again. The only objective symptom, in addition to the somnolence, was a unilateral extensor plantar reflex. That led me to the localization of the hemorrhage on one side of the brain. The patient was kept in bed for a while, and the blood was removed. While he was convalescing, deep somnolence again developed. A second operation was performed.

DR. R. A. MATTHEWS: I should like to ask the authors what role they believe trauma plays in the production of this type of hemorrhage. This question is important from the medicolegal standpoint.

DR. F. H. LEWEY: It is gratifying to the pathologist that the authors stress the relationship between high blood pressure and subarachnoid hemorrhage rather

than speak in a loose fashion of congenital aneurysm. There is no doubt about the frequency of arteriosclerotic aneurysm, whereas the question of congenital aneurysm deserves serious reconsideration. Aneurysm of the type under discussion has not been observed anywhere in the body but intracranially. Hence, it may be safer for the time being to look for arterial disease in cases of such an aneurysm than to rely on an assumption with so little foundation.

DR. J. C. YASKIN: With regard to the question raised by Dr. Gordon, somnolence is not the outstanding symptom in my experience with perhaps 150 or 200 cases of subarachnoid hemorrhage. The outstanding symptom is drowsiness in the presence of persistent severe headache. The patient, if conscious enough, will say, that a headache suddenly developed, as if somebody had struck him with a hammer on the back of the head. From then there may be moaning and somnolence, which are not by any means constant. I should not like to make somnolence a criterion of subarachnoid hemorrhage, for the pain and the meningeal signs are the outstanding features.

In reply to Dr. Matthews' question regarding the relation between trauma and subarachnoid hemorrhage, I am convinced that I have seen cases in which "spontaneous" subarachnoid hemorrhage was initiated by lifting of heavy objects. Trauma per se will never cause spontaneous subarachnoid hemorrhage. There must be the factor of preexisting vascular disease. The trauma constitutes an exciting or aggravating factor and must be severe to constitute such a factor. Often the cause is just as much a legal as a neurologic problem.

Bilateral Thrombosis of the Posterior Calcarine Arteries with Sparing of Macular Vision. DR. P. ROBB McDONALD.

A case of bilateral hemianopia caused by bilateral thrombosis of the calcarine arteries is presented. The patient had as his only complaint complete loss of peripheral vision. With correction vision was 6/6 in both eyes, and he read Jaeger test type 1 without difficulty. The results of neurologic and medical examinations were essentially normal. The patient had first, second and third grade fusion as tested on the synoptophore, and optokinetic nystagmus was readily elicited in all directions.

The cortical representation of vision and the vascular supply to the area striata are discussed.

It is concluded that peripheral vision is not essential for stereopsis or spatial orientation and that optic nystagmus may be elicited even if the field is reduced to about $2\frac{1}{2}$ degrees on either side of fixation. Apparently the performance of the complex visual functions are dependent on macular fixation and certain other associated pathways which are not closely associated with the cortical areas supplying peripheral vision.

DISCUSSION

DR. J. C. YASKIN: The following facts in this study are of importance to the everyday work in clinical neurology. First, in all likelihood the macular regions in the occipital pole are frequently supplied by branches of the middle cerebral rather than branches of the posterior cerebral artery. This is important because it at once fixes in mind the reason that with lesions in the temporal lobe there is complete hemianopia, whereas with lesions of the occipital lobe there is frequently sparing of the macula.

Second, the development of sudden blindness unaccompanied by any disturbances in the pupil or fundus occurring in an otherwise apparently healthy person need not mean that the condition is hysterical. I have seen cases in which a malignant growth with metastases in the occipital lobe was diagnosed as hysteria by competent ophthalmologists.

Recently my associates and I had a patient in our service who was totally blind for two and a half weeks but who regained his sight and then exhibited homonymous hemianopia. It appears that in some cases lesions in the region of the posterior cerebral artery or of the basilar artery may give rise first to complete blindness and later to hemianopic cuts.

Cortical Premotor and "Postmotor" Foci Which Influence the Gastrointestinal Tract and Their Efferent Pathways. DR. E. A. SPIEGEL, DR. M. J. OPPENHEIMER and DR. K. R. WESTON, Allentown, Pa.

In the dog the gastrointestinal tract may be influenced not only from the premotor area of the brain (Brodmann's area 6), as demonstrated by Fulton and his school, but from a second focus in a "postmotor" region (areas 5 or 3). Reactions of the gastrointestinal tract may be obtained in some animals only from one of these areas (either the premotor or the postmotor); in other animals this system can be influenced from both foci. Simultaneous records from the stomach, the small intestine and the colon showed that the whole gastrointestinal tract may receive impulses from the premotor as well as from the postmotor area. The effect may be synergic in all parts of the gastrointestinal system, or increase of activity in one part (e. g., the small intestine) may be associated with inhibition in other parts (e. g., the stomach and colon) of the gastrointestinal system. Sometimes, however, the effect is restricted to a limited part of this system. The variability of the effects obtained by stimulation of a certain focus seems at least partly due to peripheral factors, such as the degree of distention of the smooth muscle.

In a second series of experiments, circumscribed chronic lesions were placed in the postmotor area, and the descending pathways were studied by the Marchi method. After such lesions were placed, particularly in area 5-b, degenerating fibers could be traced through the internal capsule and then into the cerebral peduncle and were also well demonstrable in the pyramidal tract in the rostral part of the pons. The pyramidal tract in the medulla oblongata, as well as the lateral column of the cord, contained distinctly fewer degenerating fibers. This suggests that a part of the degenerating fibers observed in the cerebral peduncle conduct impulses to rhombencephalic nuclei. This interpretation is supported by the fact that some degenerating fibers coursing in a ventrodorsal direction could be seen in the cranial part of the pons dorsomedial to the pyramidal tract. The further course of these fibers could not be traced, probably because they lost their myelin sheaths after entering the tegmentum pontis. In his monograph on the centers of the autonomic nervous system, one of us (Spiegel) called attention to the close topographic relationship existing between cortical areas from which various internal organs can be influenced and the foci from which the adjacent skeletal muscles can be excited. This topographic relationship led him to the assumption that corticofugal impulses to autonomic structures may be conducted at least partly by fibers joining the pyramidal system, and partly by extrapyramidal tracts. In the present study, degenerating fibers originating in cytoarchitectonic areas from which the gastrointestinal system may be influenced were traced into the pyramidal tract. Thus, the anatomic basis has been furnished for a pyramidal conduction of corticofugal impulses from such cortical foci influencing a viscus which lie definitely outside the motor area proper. Further studies will have to ascertain to what extent corticofugal impulses to the gastrointestinal tract use extrapyramidal tracts and to what extent they use the pyramidal fibers demonstrated in this study.

DISCUSSION

DR. M. T. MOORE: May I ask Dr. Spiegel whether any of these animals were operated on without general anesthesia, and, if so, was there any expression of pain at the time gastrointestinal activity was evoked by cortical stimulation?

DR. A. GORDON: In connection with this work of Dr. Spiegel and his associates, I wish to state that the work of many physiologists, such as Schiff, Rokitsky, Claude Bernard and Brown-Séquard, on the relation of the central nervous system to diseases of the gastrointestinal tract, particularly with regard to ulceration and perforation, was undertaken a long time ago. Cushing operated on various areas of the brain—the frontal lobe, the occipital region and the base. He reported that in many cases he observed ulceration of the stomach at autopsy. Brown-Séquard cauterized the cortex and later noted perforation of the stomach and the upper

part of the duodenum. Beattie, I believe, stimulated the tuber and accelerated the rate of digestion resulting in ulcer of the stomach.

All these experiments on various areas of the brain, from one pole of the brain to the other, and on the hypothalamus also show there is a relationship between the central nervous system and the condition of the gastrointestinal tract. This work of Dr. Spiegel and his associates is exceedingly important, and indeed valuable.

Cushing advised strongly in every case of a pathologic condition of the brain, before operative procedures were undertaken, that the condition of the gastrointestinal tract be examined.

How can such a relationship be explained? The consensus of the investigators that I have mentioned is that effect is through the hypothalamus, and from the hypothalamus directly on the vagus nerve; indeed, experiments have been carried out in which stimulation of the vagus nerve produced ulceration.

I do not know what Dr. Spiegel's opinion is in regard to that question. I should like him to state whether he believes, too, that the center for gastrointestinal activity is really in the hypothalamic region. I recall some experiments not long ago on the peripheral nervous system and the upper part of the medulla in which similar conditions were observed in the stomach and the upper part of the small intestine.

DR. E. A. SPIEGEL: Dr. Moore brought up an interesting question. It has been observed that abdominal pain may occur sometimes in patients with disease of the parietal lobe. It is not improbable that abdominal pain in such diseases is due to intestinal spasm elicited by stimulation of corresponding areas. But I cannot give definite proof for such an assumption, since our animals either were under anesthesia induced with morphine and chloralose (a compound of chloral hydrate and dextrose) or were curarized. Our records show only that reactions of the smooth muscle of the intestinal tract occur on stimulation of the areas indicated and that these reactions may sometimes be accompanied by changes in respiration.

Various problems are involved in Dr. Gordon's remarks. I am a little skeptical about the relationship between lesions of the various parts of the central nervous system and gastric ulcer. So-called ulcers have been produced from so many parts of the central nervous system that it is difficult to see which part really has an effect. What the various investigators produced was usually acute erosion, and not a real ulcer corresponding to the chronic ulcer in man. I do not deny that in the production of ulcer of the stomach in man some neurogenic factor is involved. The nervous system may play an important role in the pathogenesis of the ulcer, but I am skeptical about the interpretation of some observations which tend to show that a specific area of the brain is responsible for the genesis of ulcer of the stomach in man.

I do not deny that the hypothalamus has an influence on gastrointestinal motility. That has been shown by a great many investigators, but I think that the conduction of corticofugal impulses to the vegetative system is only partly by way of the hypothalamus. In other words, two groups of corticofugal pathways must be distinguished: one conducting by way of the hypothalamus and one conducting outside the hypothalamus.

In accordance with the theory outlined in my monograph, Wang and Lu found that one can destroy the hypothalamus and still get a reaction of the sweat glands on stimulation of the cortex. In experiments with Dr. Hunsicker I observed reactions of the bladder and the vasomotor centers on cortical stimulation after cutting the chief efferent fibers of the hypothalamus. While Kabat, Magoun and Ranson only occasionally obtained reactions of the bladder on stimulation of the internal capsule, probably owing to the pentobarbital anesthesia used, Langworthy and Kolb noticed a rise in vesical pressure on stimulation of the internal capsule, the cerebral peduncle and the pyramidal tract in the oblongata, and Langworthy and Richter obtained an increase of activity of the sweat glands from stimulation of the corticospinal and the rubrospinal tract.

Book Reviews

Encephalography. By E. Graeme Robertson. Price \$5. Pp. 105, with 68 illustrations. Melbourne, Australia, and London: MacMillan & Co., Ltd.; New York: G. E. Stechert & Company, 1941.

The book consists of ten chapters and is 105 pages in length. Chapter 1 is devoted to the introduction, and in it is recorded the case reported by Luckett in 1913, in which the ventricles were filled with air after a fracture of the skull. Then the early reports on ventriculography and encephalography by Dandy are recorded *in extenso*.

Chapter 2 is devoted to the technics of encephalography and is divided into three parts: (1) the recognition of suitable indications; (2) the efficient conduct of the actual procedure, and (3) the interpretation of the results. The author mentions the usual indications and contraindications for the procedure. In figure 5a the author shows the roentgenogram being made with an assistant holding the cassette. The assistant is entirely unprotected from the roentgen rays, and this practice must be condemned. The roentgenographic technic as described by the author utilizes a number of unorthodox positions and appears laborious, inasmuch as he states that taking the encephalogram requires from sixty to ninety minutes. Lateral stereoscopic views are obtained only with the patient in the horizontal position; these are not sufficient, in the reviewer's opinion, for proper roentgenographic study.

Chapter 3 is devoted to the technical results and is based on the analysis of 208 cases. In 7 cases the air did not enter the ventricles. The patients had the usual reactions, and the author believes that the procedure has no therapeutic value. Three patients in the series died. One of them had an astrocytoma of the right temporal lobe and another an aneurysm of the middle cerebral artery. It was not thought, however, that encephalography was responsible for the patient's death. No diagnosis was made in the third case.

Chapter 4 is devoted to the route taken by the air and the anatomic considerations. The distribution of the air in the intracranial cavity and how it is affected by alterations in the position of the patient's head are fully described and portrayed in the accompanying illustrations.

Chapter 5 is devoted to a study of the fourth ventricle. The author first describes the anatomy of this cavity and its relation to the brain stem and the cerebellum and then its appearance as seen in the pneumoencephalogram with the patient's head in various positions.

In chapter 6 the aqueduct of Sylvius is described, first anatomically and then as it appears in the roentgenogram. A case of stenosis of the aqueduct is reported, and from the appearance of the calcium shadow in figure 38a it is likely that the lesion was due to toxoplasmic encephalitis.

The third ventricle and its encephalographic anatomy are considered in chapter 7. A number of illustrations of the third ventricle as seen in various views of the head accompany this chapter. The lateral ventricles are then considered, and the various portions of these cavities are described, primarily as they appear in the pneumoencephalogram. The distortion of the ventricular system as produced by tumors of the cerebral hemisphere is then discussed. The author properly calls attention to the fact that in a small percentage of cases an intracranial tumor may exist without recognizable deformity of the ventricular system. Post-traumatic conditions are discussed, such as subdural hematoma and enlargement of the lateral ventricles. A small section is devoted to the size of the ventricles. Under the heading of epilepsy, the author points out that frequently the lateral ventricles are asymmetric. Then follows a discussion of degenerative, atrophic and aplastic lesions of the brain, as visualized in the encephalogram, together with the etiology of these changes in the brain.

Chapter 9 is devoted to the presence of air in extraventricular positions. The appearance of gas in the subarachnoid space, first over the cerebellum and later in the various basal cisterns, is discussed. Lastly, the gas in the subdural space is described as it is seen beneath the tentorium and over the cerebral hemispheres.

It is the belief of the reviewer that the author has covered too much subject matter in this small edition. Another criticism is that the figures, practically without exception, have been retouched too much.

The monograph, for the most part, is well illustrated and contains a sound description of pneumocephalography and its uses.

A Text-Book of Neuro-Anatomy. Third Edition. By A. T. Kuntz, Ph.D., M.D. Price \$6. Pp. 518, with 317 illustrations. Philadelphia: Lea & Febiger, 1942.

The third edition of this text is, like the previous ones, written for the use of the medical student. The outstanding feature of the book is simplicity and clearness of presentation. The didactic point of view is always stressed, and each chapter is concluded with a summary. The danger that a student might give more attention to the summary than to the preceding, more elaborate presentation is counterbalanced by the advantage that is gained by the stressing of important factors and the subordinating of details.

In the first two chapters, which show no changes as compared with previous editions, the author succeeds in describing in thirty-nine pages the evolution, comparative anatomy and ontogenesis of the nervous system in an exceedingly clear, simple and, at the same time, comprehensive manner. These chapters are followed by a short description of the gross anatomy of the central nervous system. Here the author breaks away from the traditional manner of initiating the study of the nervous system with the microscopic elements and the neuron theory. His method is more in line with modern pedagogic methods, stressing the whole and the *Gestalt*. Subsequently, however, the histogenesis, the neuron and the interstitial tissues are described, although in a not very detailed manner. Discussion of the reflex and correlation mechanisms in the spinal cord and brain stem precedes the description of the long conduction pathways, which are presented in their functional relationships.

The diencephalon and the thalamic connections are discussed in greater detail here than in the previous editions.

In the chapter on functions of the cerebral cortex the author attempts to give a summary of the present knowledge of aphasia, a discussion of which hardly belongs in a textbook of neuroanatomy for medical students. The presentation is necessarily schematized and must be confusing to those who lack clinical knowledge and experience.

As in the previous editions, the illustrations are not up to modern standards. A large percentage are taken from various sources. Many of the diagrams are overcrowded and difficult to follow at the magnification given. The usefulness of this otherwise truly valuable, and in many respects original, book could be increased by the adoption of more modern illustrative techniques.

Mental Illness: A Guide for the Family. E. M. Stern and S. W. Hamilton. Price \$1. Pp. 152. New York: The Commonwealth Fund, 1942.

This little book is written for the sake of the families of patients afflicted with mental disease. It consists of a brief account of the phenomena of mental disease, the methods of diagnosis, the legal procedures involved and a discussion of hospitalization as seen by the family. Relatives are urged to make representations to the officials in charge of the hospital in case of apparent neglect or abuse and to join local and national organizations for the furtherance of mental hygiene. Useful tables giving information concerning the local provisions for the mentally ill in various states are presented.

Copies of the book may be purchased in quantities at low cost for distribution to relatives by institutions.

GROUPING BEHAVIOR OF NORMAL PERSONS AND OF PERSONS WITH LESIONS OF THE BRAIN

FURTHER ANALYSIS

WARD C. HALSTEAD, PH.D.

AND

PAUL H. SETTLAGE, PH.D.*

CHICAGO

In an investigation of grouping behavior in patients with cerebral lesions and in normal persons, Halstead¹ found both quantitative and qualitative deviations from the normal in the performances of certain patients with cerebral injury. It was found, for example, that patients with a primary lesion in either the right or the left frontal lobe (1) employed fewer objects "spontaneously" from a field of 62 test objects in response to the instruction to place those together which "seem to belong together"; (2) recalled fewer objects after an interval of five minutes; (3) manifested little or no differential recall of grouped as opposed to ungrouped objects; (4) produced a smaller total number of groups, and (5) deviated characteristically in the distribution of the types of groups created, as determined by an adaptation of Klüver's method of equivalent and nonequivalent stimuli. This work, based on neurosurgical cases, seemed to indicate that various organizing principles, such as "shape," "size" and "color," employed in dealing with multiple objects or events may be rendered differentially available by damage to the brain.

In the present investigation further analysis has been made of grouping behavior in normal subjects and in persons with injury to the

* Fellow of the National Research Council 1938-1939; now of the Department of Psychology, Brooklyn College.

Read at the Ninety-Seventh Annual Meeting of the American Psychiatric Association, Richmond, Va., May 7, 1941.

From the Otho S. A. Sprague Memorial Institute and the Division of Psychiatry, Department of Medicine, University of Chicago.

1. Halstead, W. C.: (a) Behavioral Effects of Lesions of the Frontal Lobe in Man, *Arch. Neurol. & Psychiat.* **42**:780-783 (Oct.) 1939; (b) Preliminary Analysis of Grouping Behavior in Patients with Cerebral Injury by the Method of Equivalent and Non-Equivalent Stimuli, *Am. J. Psychiat.* **96**:1263-1294, 1940.

brain. The test situation in this investigation differed in certain essentials from that previously employed by Halstead: (1) Geometric figures were used in place of actual objects; (2) the test figures were presented serially to the subject by means of a special apparatus, and (3) the subjects worked with a knowledge of their "successes" and "failures" (since the apparatus was set to respond to "correct" choices only).

APPARATUS, TEST MATERIALS AND PROCEDURES

Apparatus.—The apparatus consisted essentially of an electrically controlled exposure device for serial presentation of groups of two dimensional test figures and an associated keyboard providing a multiple response situation for the subject. Each correct response of the subject automatically resulted in the presentation of another set of test figures by the apparatus.

The test figures for each test employed were prepared on a separate strip of white holland cloth, which in operation was attached to the outer circumference of a metal drum. An electrical escapement mechanism, controlled by a bank of four switches located below a viewing window, activated the drum in stepwise fashion about its horizontal axis. A limiting aperture and the viewing window placed before the drum restricted the field to the test figures of a single item for any given position of the drum. As brought to sharp focus by a 2.5 power reading lens, the test figures averaged approximately 3 by 3 degrees of visual angle bidimensionally for the subject.

Incorporated in the apparatus was a stylograph, with five signal magnets. One signal magnet corresponded to each release switch, and each magnet registered a signal every time the corresponding switch was thrown, regardless of whether or not the switch was in the effective tripping circuit at the moment. The fifth signal magnet registered a signal every time the release mechanism was activated. The stylograph paper, driven by a synchronous motor, provided a graphic record of the operation of every switch, the order in which the switches were operated, the "correctness" of the response and the partial and total time intervals involved.

Test Materials.—In devising the test materials our general purpose was to present groups of test figures that would normally be dealt with spontaneously in terms of certain categories or organizing principles.

A photograph of the test figures comprising the 9 tests, adopted as a standard series after considerable preliminary work with normal subjects and a number of subjects with cerebral lesions is presented in figure 1. The following brief description of the various tests requires frequent reference to figure 1.

TEST 1.—Roman Numerals: This test is intended to serve primarily as a practice test which would make it possible to keep verbal instructions at a minimum. Each Roman numeral of test 1 corresponds to the number of the key which operates the machine for that trial. For example, in the first item of test 1 the Roman numeral I can be seen through the viewing aperture. The "correct" response of the subject consists in throwing the switch which is labeled I. When this is done the second item of test 1, the Roman numeral III, is exposed. When the subject operates the switch labeled III, the mechanism is tripped and the next item is exposed, etc. The four switches are labeled from the left to the right, with switch I placed at the subject's left as he views the test items.

TEST 2.—Number of Objects: In general, an effective cue to the "correct" key is provided by the number of objects or signs present in any given test item. For example, the four manikins in the eighteenth test item indicate that the fourth key is to be pressed, and the three plus signs opposite number 28, in the left column, indicate the third key. (The interpretation of figure 1 will be clearer if it is remembered that the key indicated by any given Roman numeral of test 1 is also the correct key for all presentation items on the same horizontal line;

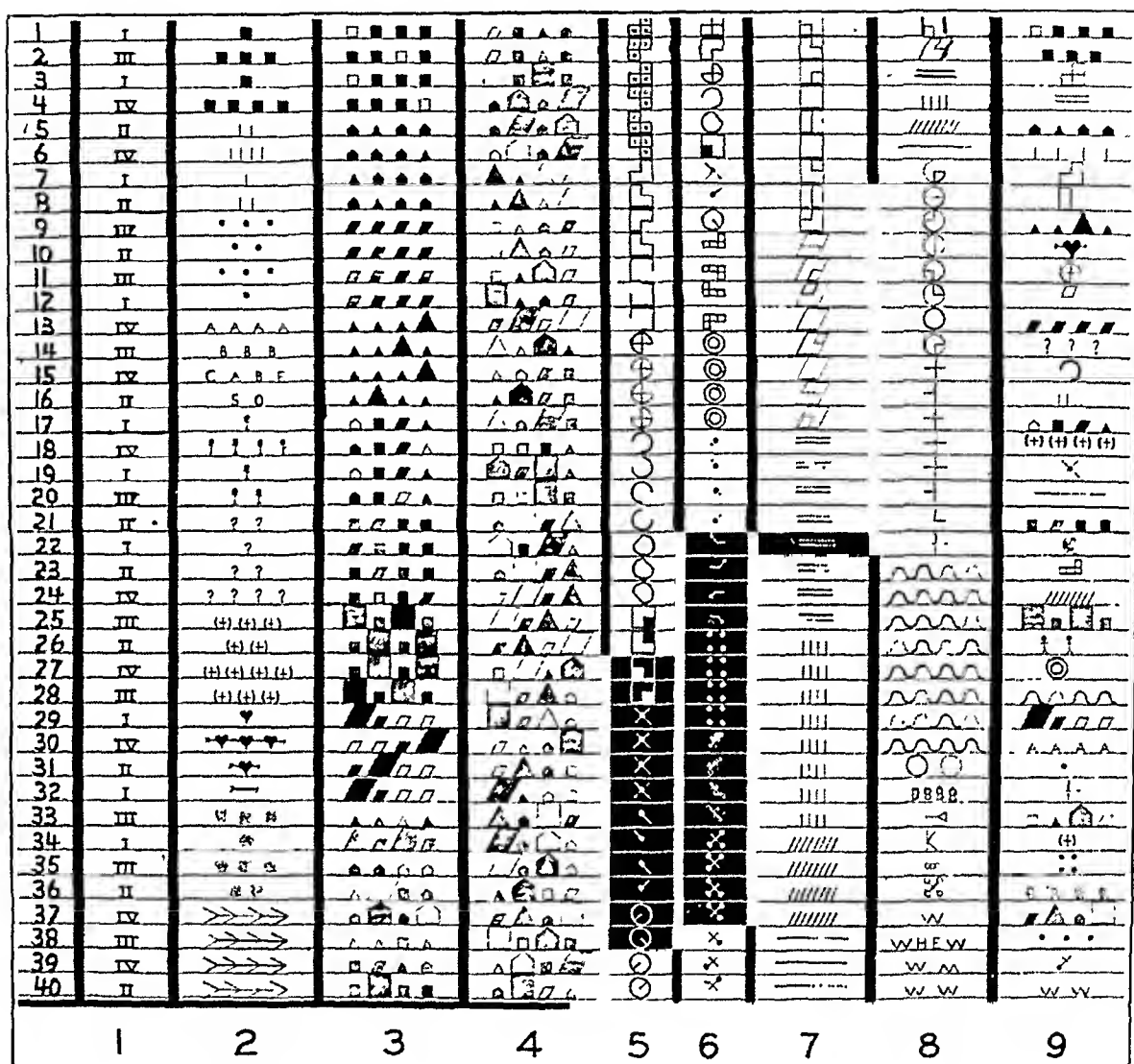


Fig. 1.—Photograph of test figures, reduction $\times 5$. The 40 items of each numbered vertical column constitute an individual test. Each item was exposed separately (see text). The correct key or switch (of four) on the multiple choice apparatus corresponding with the items of each of the 9 tests (i. e., the horizontal rows above) also corresponds with the Roman numeral test figures of test 1.

that is, the same key corresponds to all test items opposite any given arabic numeral. Hereafter we shall refer to the test items by number; e. g., the letters SO in test 2 will be referred to as item 16, test 2.) Items 37, 38, 39 and 40 in test 2 were composed of red and black lines in the original test material. It was

intended that the number of black lines in any one of the arrow-like figures should serve as an effective cue—two black lines: the second key, etc.

TESTS 3 and 4.—Oddity: These tests may be designated as oddity tests. One of the four figures in each presentation space differs from the three others in a certain characteristic, and the position of the odd figure gives the clue as to the correct key. Oddity always occurs in one of four characteristics: solid outline (items 1 to 4, 17 to 20, 33 and 37 in test 3, and items 1 to 3, 13, 17, 21 to 23, 33 and 37 in test 4); shape (items 5 to 8, 21 to 24, 34 and 38 in test 3, and items 4 to 6, 14, 18, 24 to 26, 34 and 28 in test 4); color² (items 9 to 12, 25 to 28, 35 and 39 in test 3, and items 7 to 9, 15, 19, 27 to 29, 35 and 39 in test 4), and size (items 13 to 16, 29 to 32, 36 and 40 in test 3, and items 10 to 12, 16, 20, 30 to 32, 36 and 40 in test 4).

The items of these two tests are graded in difficulty. The odd figure in the items of the first part of test 3 is perceptually striking. As one proceeds through the latter part of test 3 and then through test 4 the perceptual prominence of the odd figure diminishes, and for continued correct responses this test seems to demand a shift toward a logical-verbal procedure in discovering the odd figure. Perceptual oddity is progressively obscured in successive exposures during these two tests by the introduction of additional characteristics. If one considers the first 16 items of test 3, one finds that if oddity is present in the solid outline characteristic, the figures are all alike in color, size and shape; if oddity occurs in the shape characteristic, the figures are all alike in color and size and are all solid, etc. Items 17 to 40 in test 3 all contain one additional feature; i. e., if oddity is present in the shape characteristic, there are differences in the figures in one of the other characteristics (e. g., color, items 21 to 24; size, item 34); if oddity occurs in the size characteristic, differences exist among the figures in respect to color, shape or solid outline. In the first part of test 4, additional differences are present in two features, and in the last part of test 4 all four variables are represented in each item, but true oddity occurs in only one.

TESTS 5 and 6.—Quadrant: Each figure includes a characteristic which signifies or points to one of the four possible quadrants. The quadrants are arbitrarily numbered in a clockwise direction, beginning with no. 1 at the upper left. In order successfully to complete these tests the subject must grasp the principle of quadrant arrangement and must further associate each of the four quadrants with one of the four keys. The quadrant arbitrarily numbered I corresponds to the first key; the quadrant number II corresponds to the second key, etc.

The cue embodied in the items of tests 5 and 6 is quite unmistakable, except in items 29 to 32, test 5, and figures 10 to 13 and 26 to 29, test 6. The central disk and three of the radiating lines in items 29 to 32, test 5, are green, whereas the fourth radiating line is black. The fourth black line indicates the significant quadrant. The correct cue is obtained from items 10 to 13, test 6, by regarding the fourth offset square as being situated in one of the four quadrants. Items 26 to 29, test 6, contain three green disks and one black disk. The color difference is not well represented in figure 1, although the reader can infer the position of the black disk from the knowledge that its position indicates the significant quadrant.

2. The colors used in the original test materials (black, red, green, blue and orange) are reproduced as shades of gray in figure 2. By knowing which key is the correct one for each of the items in tests 2 and 3 (compare test 1) significant color differences in specific figures may be inferred.

TESTS 7 and 8.—Part-Whole: Key I is indicated if one fourth of the figure, or of the number of lines, is composed of solid lines, the remainder consisting of dotted lines. If one half is in solid lines, key II is indicated; if three fourths is solid, key III is indicated, and if the entire figure (or all the lines) is solid, key IV is correct.

TEST 9.—Recognition: The final test was made up of a selection of items taken from tests 2 to 8. The material in test 9 is identical with or similar to corresponding items in the other tests.

Procedure.—The procedure consisted essentially of securing "spontaneous" responses of the subject to the 40 test items in each of the 9 tests described in the foregoing section. Each test was presented separately and in numerical sequence from test 1 through test 9.

The subject was seated in front of the apparatus, the height of which was then adjusted to permit full and clear vision of the presentation material. With item I of test 1 present in the viewing aperture, brief instructions were given:

"You have seen switches like this before. They are ordinary light switches [examiner turns the four switches on and off in succession]. The machine isn't running now; so nothing happens when I turn on the switches. Now I turn on the machine. Now, if you press the correct key, this figure which you see [examiner points to viewing window] will disappear, and something else will take its place. Then, again, if you press the correct key, there will be another change, and so on. Each time, only *one* of the four keys will make it move. If you press any of the three wrong keys, nothing will happen; so you will know whether or not you were right. Now, what you see in here always tells you somehow which key is the right one. It gives you a clue or a hint, and what I want you to do is to try to discover the nature of that clue or hint. If you discover it, you will be able to press the right key every time—to make the figure move every time you press a key. You can take all the time you want. The object is to press the right key as often as possible."

In giving these instructions, an effort was made to suit the language of the instructions to the subject. Questions coming from the subject were answered insofar as they bore on the foregoing instructions. Frequently the subject asked whether the number I that he saw meant that he should press a certain key, and then he was told that that was exactly what we wanted him to determine. Subjects were allowed to continue unaided in their solutions of the tests, within the time limit set by the experimenter. Whenever the experimenter undertook to aid the subject, he proceeded by giving at first vague hints and by making more and more obvious suggestions as the subject's performance failed to improve. A careful record was kept of all helps which were given. In some cases the conversation between the experimenter and the subject, during part or all of an experimental session, was recorded on a phonograph. Whenever this was done, the subject was encouraged to verbalize freely.

SUBJECTS

Normal Control Subjects.—The results obtained with a group of 10 normal subjects form the basis for the graphic presentation of results for normal persons as indicated in figures 3 to 8. This group was heterogeneous as to age, sex, educational background and socioeconomic status. All control subjects were in good general health at the time they were tested and were selected primarily from the standpoint of availability.

Experimental Subjects (neurosurgical patients).—The results obtained on 6 neurosurgical patients from the series previously reported by Halstead^{1b} constitute the basis for the graphs of individual performances in figures 3 to 8. Before these results are considered, attention should be directed to the following facts concerning the experimental subjects: These operative patients represented unusually "good" or "successful" recoveries. Each patient presented only minimal local signs (if any) of the neurologic lesion; each had resumed gainful occupation or studies (in 2 instances at the college level) or preparations to that end. Each patient was in excellent general health at the time of testing. (The limits of formal intelligence were established after operation by means of one or more standard intelligence tests.) Excellent rapport during the tests had developed over a period of months or years, during which each subject had cooperated voluntarily with this laboratory in studies involving a wide range of behavior functions.

Diagrams indicating the minimal cerebral lesions for each of the 6 experimental subjects (subjects 1, 6, 10, 19, 22 and 25) are presented in figure 2. The diagrams were prepared in the manner previously described by Halstead.^{1b}

RESULTS

The number of errors made on the first attempt in each of the 9 tests provides a quantitative basis of comparison between the performances of the experimental subjects and those of the normal control group. Because of the relatively low variability in the performances of the normal subjects, the average performance of the group on each of the 9 tests has been taken as a point of reference in presenting individual profiles of the experimental subjects.

Normal Subjects.—All the 10 control subjects "spontaneously" discovered the solution in all 9 of the standard tests (fig. 2) during the first trial. This was true in spite of the fact that none of these subjects received aid or suggestions on any of the items and that the concepts employed by the subjects in solving some of the tests needed to be progressively refined or broadened to permit continued successful responses. Deviations from subject to subject in approach to the tests tended to be minor in character with reference to the total results and need not be examined here in detail.

Experimental Subjects (neurosurgical patients).—The 6 subjects who had undergone operation were from the series reported previously by one of us (Halstead^{1b}). In the interest of continuity the same case numbers (1, 6, 10, 19, 22 and 25) are employed here.

SUBJECT 1.—An American-born man aged 48, a salesman, entered the University of Chicago Clinics on Sept. 4, 1935 with a history of severe headaches, occasional vomiting, blurred vision and loss of weight. Operation, performed on September 17 by Dr. Percival Bailey, involved partial extirpation of the left prefrontal lobe for removal of a meningioma of the olfactory groove. Recovery was uneventful; the patient was discharged from the hospital on September 28.

The postoperative intelligence quotient was 110 (Stanford-Binet). The patient was strongly "right handed." Postoperative social adjustment included phenomenal "success" as a salesman.

In figure 3 the number of errors made by subject 1 on the first trial of each of the tests (completed by him) is shown graphically. The solid horizontal black line indicates the average score on each test made by the group of normal subjects; the vertical lines indicate the average variations in the normal group for the 9 tests.

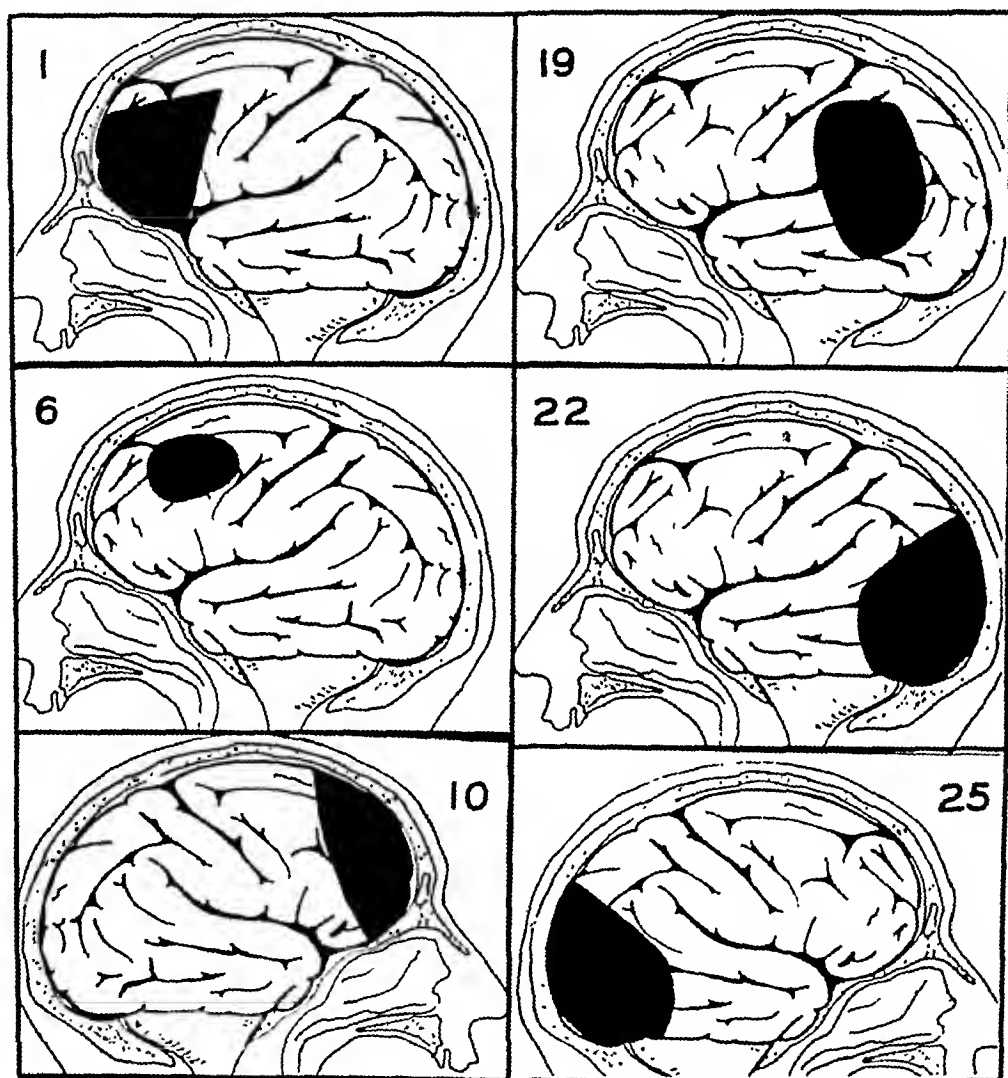


Fig. 2.—Diagrams indicating the approximate lesion (in its lateral aspect) of each of the experimental subjects. These diagrams were prepared by the method described by Halstead.^{1b} Lesions in the left hemisphere are indicated by the case number in the upper left corner of each diagram; lesions in the right hemisphere, by the case number in the upper right corner.

Quantitatively, the most striking feature of the performances of subject 1 is the fact that, with the exception of test 3, all of his scores fell outside the limits of the normal group. (His performance on test 3 indicates, however, that he could manifest a normal grasp of the task imposed by that test.) He encountered considerable difficulty at the outset with test 1. He appeared to grasp the

instructions; he selected one key after another after deliberate study of the particular figure in the window and yet did not grasp at once the fact of simple and never failing correspondence of identity between the number appearing as the figure in the window and the number of the "correct" key. During the first half of the test he appeared to have adopted an attitude of "trial and error" searching and yet gave no evidence that such experience could subsequently be utilized in solution of the general problem. This attitude was common to the normal subjects, but experience with one or two items was usually sufficient for the principle of "identical number" to emerge. After a series of errors in test 1, the subject (S) complained that the experimenter (E) was expecting "quite a bit" from some one who had been out of school a long time. The following conversation then ensued:

E: "When you get on to it you will be surprised how simple it really is."

S (looking at the figure in the window of the apparatus): "Well, now, there is number IV, but it wouldn't be the fourth key."

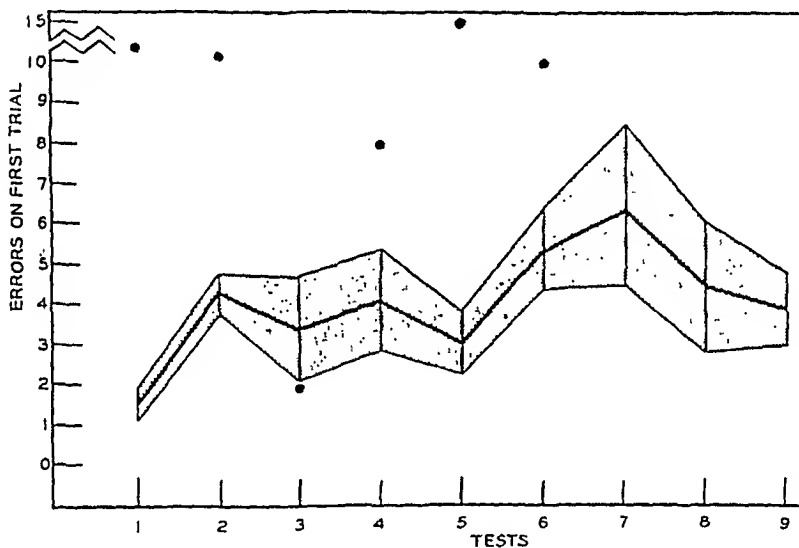


Fig. 3.—Graph indicating the performance of subject 1 (lesion in the left frontal lobe), showing the number of errors (black dots) made on the first trial on 6 of the 9 tests. The average performance of the normal control subjects in each of the tests is indicated by the profile in the lower portion of the figure (heavy black line). The average deviation of the normal subjects in each test is indicated by the limits of the shaded area.

E: "Why wouldn't it be the fourth key?"

S: "I tried that system before, but it didn't work."

Subject 1 thereupon tried key IV, which proved to be "correct." He then completed test 1 without further errors.

Soon after commencing test 5 subject 1 announced that he had discovered the solution—"the number that is missing." He used this clue successfully as long as there were three numbers and a fourth number was missing, i. e., until he came to the seventh item, which did not include any numbers and hence was not characterized by a missing number. It did not seem to occur to him that there was any kind of continuity between the first six items and the succeeding ones.

The aid offered by the examiner was at first confined to the repeated assertion that a single principle would apply to and permit the solution of all the items in the test. The subject continued to make errors, however, and the experimenter finally suggested the quadrant principle to him. From the nature of further errors made by subject 1, it was apparent that he was proceeding on the assumption that both the upper and the lower pair of quadrants should be numbered from left to right. He expressed the view, when questioned, that any other number arrangement would be wrong. Since his expressed conviction was so strong as to make it improbable that he would spontaneously entertain any other possibilities, the clockwise manner of numbering was specifically explained to him. He finally grasped the correct principle and then proceeded to utilize it as effectively as any other subject throughout the remainder of the test.

At the conclusion of test 6, subject 1 declined to continue with the remaining tests. The only reason that he would offer was: "That machine's got me buffaloeed." Attempts made subsequently to get him to complete the tests drew the same answer. It is of interest that this test situation and the Rorschach situation provided the only 2 instances of refusal of a test situation out of several hundred hours of study of subject 1 during the past five years.

SUBJECT 6.—An American-born man aged 51, of Irish descent, a traffic policeman, entered the University of Chicago Clinics on June 17, 1936 with a history of severe headaches, spells of dizziness and unsteadiness for the past four months and progressive failure of memory. Operation, performed on June 17 by Dr. Paul C. Bucy, involved partial extirpation of the left prefrontal lobe for removal of benign glioma of the septum pellucidum. Recovery was uneventful, and the patient was discharged from the hospital on July 20. The postoperative intelligence quotient was 105 (Stanford-Binet). The patient is strongly "right handed." He is a retired bachelor with a modest but comfortable income from his savings and pension. He spends his time "enjoying life" in conventional ways.

Subject 6 began test 1 (fig. 4) by systematically operating the keys in the order: 1, 2, 3, 4; 1, 2, 3, 4, etc. His statement of the solution of the test was, "It goes in a rotating fashion," and he seemed to feel that he had accomplished what was expected of him. The experimenter then emphasized that the subject was to try to make the machine trip every time he pressed a key. The subject seemed at first unable to do this, but after being questioned item by item by the experimenter in terms of "What do you see? Now which key are you going to press?" he grasped the solution and was able to utilize it without further errors. In test 2 subject 6 encountered no particular difficulty until he reached item 30, the three hearts and an arrow. Then he leaned back in his chair and studied the figure. He seemed unwilling to proceed. The following conversation ensued:

E: "What do you have there?"

S: "Three hearts."

E: "Is that all?"

S: "No; there's a string through them."

E: "Oh, three hearts and a string?"

S: "Yes."

E: "Well, could that be four things then?"

S: "Yes. Well, I suppose it's this key there" (subject chooses key IV, the "correct" key).

Subject 6 was then able to count the heart and the arrow in item 31 as two figures and to respond on that basis. On reaching item 37, the subject again

appeared unwilling to proceed further, complaining that he knew of no way to deal with the figure. It was then pointed out that the arrow-like figure could be regarded as composed of nine individual lines, that some of these lines were black and some were red and that it was possible to count separately the number of black and the number of red lines. Then, during the subject's effort with items 37 to 40, he was asked for each item: "How many black lines? Then which key are you going to press?" The "coaching" seemed to enable the subject to grasp the solution of the arrow-like figures.

In test 5 (quadrant) subject 6 encountered considerable difficulty. When the experimenter realized that the subject did not grasp the quadrant principle, he

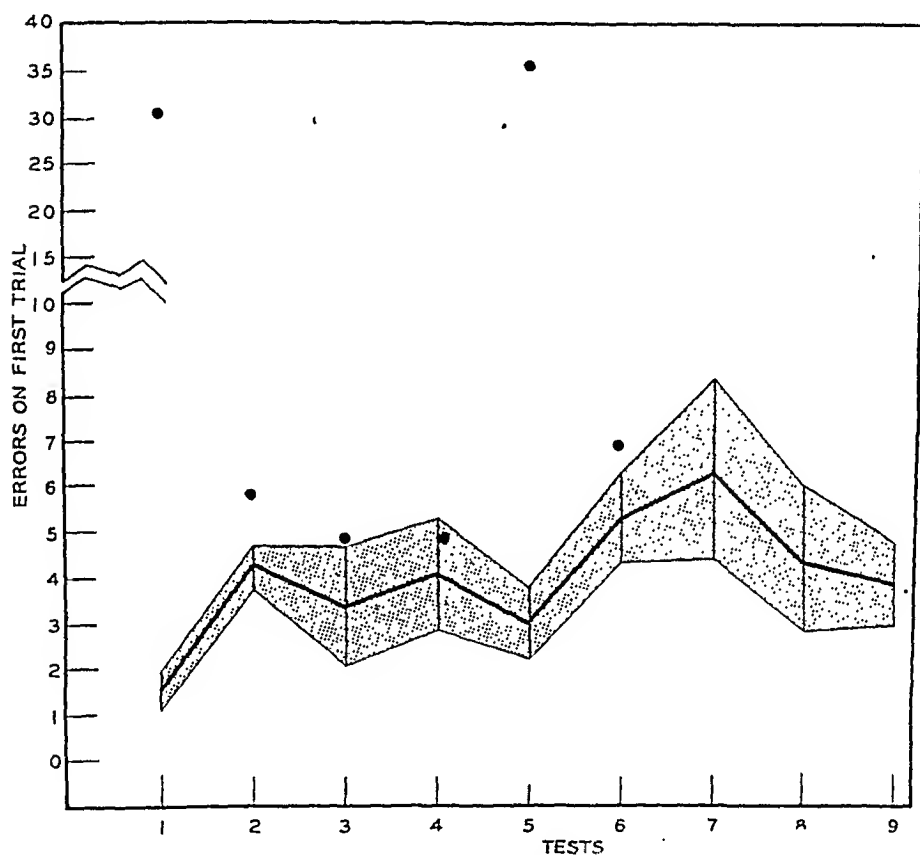


Fig. 4.—Graph indicating the performance of subject 6 (lesion in the left frontal lobe), showing the number of errors (black dots) made on the first trial in 6 of the 9 tests. The profile in the lower portion of the figure represents normal variation in each test and is the same as that in figure 3.

called it to the latter's attention. This did not improve the subject's performance, however. Finally the examiner prepared a diagram, a square divided into four parts, with Roman numerals in each quadrant. The diagram and its relation to the tests were explained. The subject was then able to solve the next few items with the aid of the diagram; when each new item appeared, he consulted the diagram and then chose the correct key. Next he was encouraged to attempt the solution without the diagram, which he was unable to do. As a last help, the examiner spoke to the subject as follows: "Can you imagine the window [pointing

to the viewing window] to be divided into four parts? Now can you imagine the number I to be here in the upper left, the number II in the upper right, the number III in the lower right and the number IV in the lower left?" At this point subject 6 seemed to grasp the principle and then completed the remaining items of test 5 without error.

As in the case of subject 1, test 6 (quadrant) was the last in the series to be completed by subject 6. He insisted that the tests were too difficult and strongly urged that he not be asked to do more of them.

SUBJECT 10.—An American-born woman aged 31, a housewife, entered the University of Chicago Clinics on July 24, 1939 with a history of severe throbbing headaches and numbness and tingling of the upper and lower extremities during the past six months. Operation, performed on July 29 by Dr. A. Earl Walker, involved partial extirpation of the right prefrontal lobe for removal of a cerebral

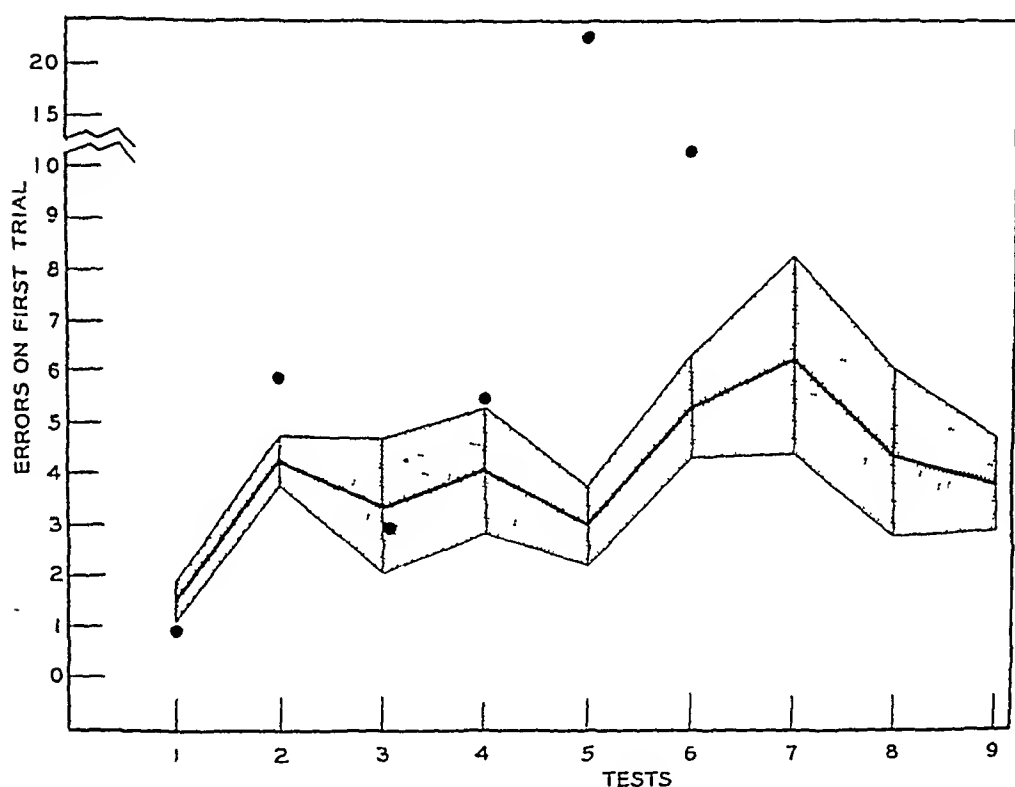


Fig. 5.—Graph indicating the performance of subject 10 (lesion in the right frontal lobe), showing the number of errors (black dots) made on the first trial in 6 of the 9 tests. The profile in the lower portion of the figure represents normal variation in each test and is the same as that in figure 3.

aneurysm. Recovery was uneventful, and the patient was discharged from the hospital on August 15. The preoperative intelligence quotient was 120 (Stanford-Binet), and the postoperative quotient was 124 (Stanford-Binet L). The patient is strongly "left handed." She manages a home with two children and a partially invalided husband, much as she did prior to her operation.

The general approach of subject 10 to the test situation in terms of prompt grasp of the instructions, general attitude and general mode of procedure in the first part of the series of tests could not be distinguished from that of the normal subjects. In test 5 (quadrant), however, she encountered considerable difficulty (fig. 5), making a total of 23 errors, as compared with the average of 3 errors

made by the normal subjects. In spite of the fact that the principle of the test was explained to her by means of a diagram, her performance did not materially improve.

On test 6 (quadrant) subject 10 made twice as many errors as the average normal subject in spite of the fact that the quadrant principle had been explained in test 5. The general nature of subject 10's performance may be illustrated with reference to items 18 to 20. These items, each composed of three dots of decreasing size, were normally usually envisaged as pointing in the direction of one of the quadrants made effective in the preceding items. Some of the normal subjects were uncertain, on first encountering these items, as to which of two diagonally opposite quadrants the dots might indicate, but all of the normal subjects were able to discover the correct solution in a short time and without aid. Subject 10, on the other hand, was at first unable to think of any way of dealing with these figures. Item 18 was resolved after trial and error had eliminated all keys but the correct one, but no possible explanation occurred to the subject. On item 19, the experimenter ventured to help to the extent of asking the subject how the item differed from the previous one. The fact that the subject was able to say, "They're the same, but reversed" did not suggest to her an interpretation in terms of the quadrant principle. The first hypothesis that suggested itself to the subject came when she was attempting to deal with item 19. She suggested that it might be key IV because "the large dot could contain four small ones."

When the subject showed no sign of discovering the solution by the time item 21 was reached, the experimenter undertook to offer help. This conversation took place:

E: "Before this you worked on the idea of four corners."

S: "Yes, but here I don't have four corners."

E: "Could you consider that they point in a certain direction?"

S: "Yes."

The subject then chose the correct key and said, "They work out when you consider them that way."

At the request of the subject, the series was terminated with test 6. She was considerably disturbed with her performance. In spite of the fact that repeated assurance was given that she had "done well," she voiced dislike for the tests and stated that she wanted to "stay away from them."

SUBJECT 19.—An American-born youth aged 19, a student, entered the University of Chicago Clinics on Jan. 15, 1936 with a history of a fall at the age of 5 years, which resulted in a compound depressed fracture of the skull, repaired by operation. After the fracture, the patient was unable to speak for one week; he experienced severe weakness of the right arm and leg, which continued. Generalized jacksonian seizures began at the age of 13 years, and these persisted. Operation, performed on January 24 by Dr. Paul C. Buey, involved partial extirpation of the left parietal and temporal lobes for removal of a cortical scar. Recovery was uneventful; the patient was discharged from the hospital on February 11. The postoperative intelligence quotient was 110 (Stanford-Binet L). The patient was strongly "right handed" in childhood, but weakness of the right arm and hand had necessitated the development of functional "preference" for the left hand. He was graduated from a large metropolitan high school after his first operation and at present is a student in an art school. He has occasionally shown "spiking" and 3 per second waves in his electroencephalogram, but these were not present at the time of the last determination.

As may be seen in figure 6, subject 19 made fewer errors than the average normal subject on 6 of the 9 tests. He grasped the instructions at once and made no errors on test 1. He worked slowly and deliberately, with no help from the experimenter. He expressed a lively interest in the tests and has since cooperated readily in repeating the tests. It should be noted that, in contrast to the preceding subjects, subject 19 had a visual field defect (right homonymous hemianopia of *vue nulle* type ^{2a}), in addition to defective ocular movements.³ In general, his performance on the series of tests was superior to that of any of the normal subjects.

SUBJECT 22.—An American-born woman aged 25, a filing clerk, entered the University of Chicago Clinics on Sept. 27, 1937 with a history of visual disturbances during the past ten years, consisting of flickering lights and colors, and headaches and spells of vomiting for the past eighteen months. Operation, performed on October 23, by Dr. Paul C. Bucy, involved complete extirpation of the left

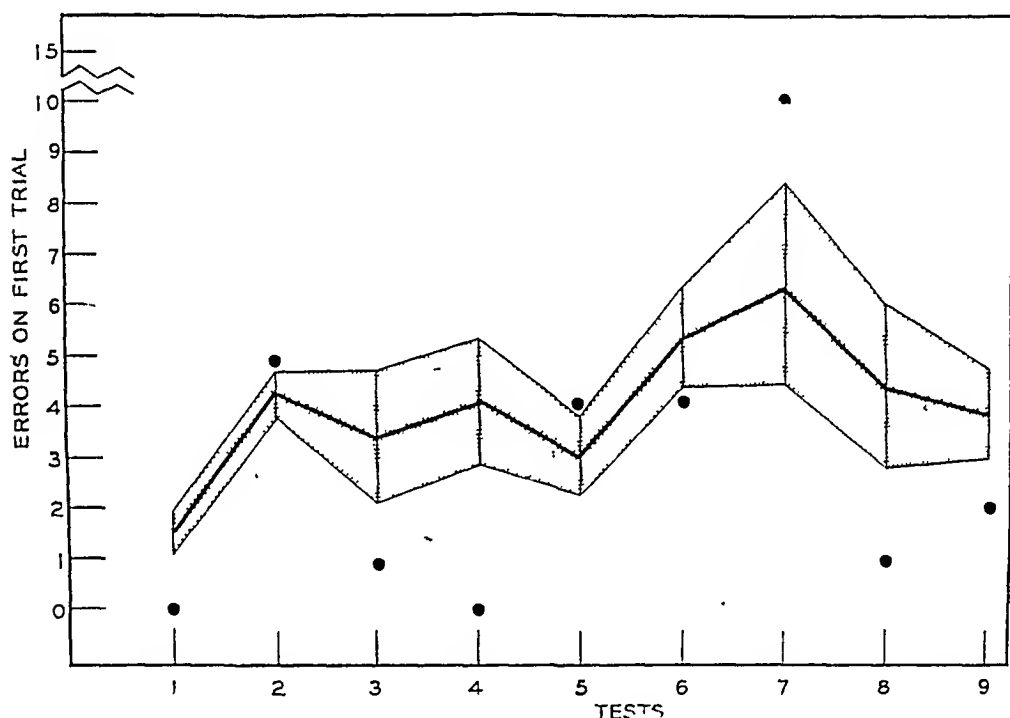


Fig. 6.—Graph indicating the performance of subject 19 (lesion in the left parietotemporal region), showing the number of errors (black dots) made on the first trial in each of the 9 tests. The profile in the lower portion of the figure represents normal variation in each test and is the same as that in figure 3.

occipital lobe for removal of a spongioblastoma polare. Recovery was uneventful, and the patient was discharged from the hospital on November 11. The post-operative intelligence quotient was 115 (Stanford-Binet). The patient was strongly "right handed." She secured employment for herself in a factory after her operation and has worked steadily since.

As may be seen in figure 7, subject 22 had only normal difficulty with test 1. She grasped the instructions promptly and, after making two errors at the outset,

2a. *Vue nulle*, as opposed to *vue noire*. No scotomatous area was present.

3. Halstead, W. C.: A Method for the Quantitative Recording of Eye Movements, *J. Psychol.* 6:177-180, 1938.

proceeded without making further errors on this test. Likewise, her performance on tests 8 and 9 did not differ greatly from the average normal performance. Her performance on the intervening tests differed widely from the normal, however. In contrast to subjects 1, 6 and 10, the errors made by subject 22 did not seem to disturb her in the least. She worked steadily at each of the tests, seeking no assistance from the experimenter. She was permitted to go through all 9 tests without assistance of any kind. Her interest and attitude toward the tests did not differentiate her from the normal subjects. An analysis of various visual functions of subject 22 has been reported by one of us (Halstead) elsewhere.⁴

SUBJECT 25.—An American-born woman aged 22, a stenographer, entered the University of Chicago Clinics on Sept. 27, 1939, with a history of severe head-

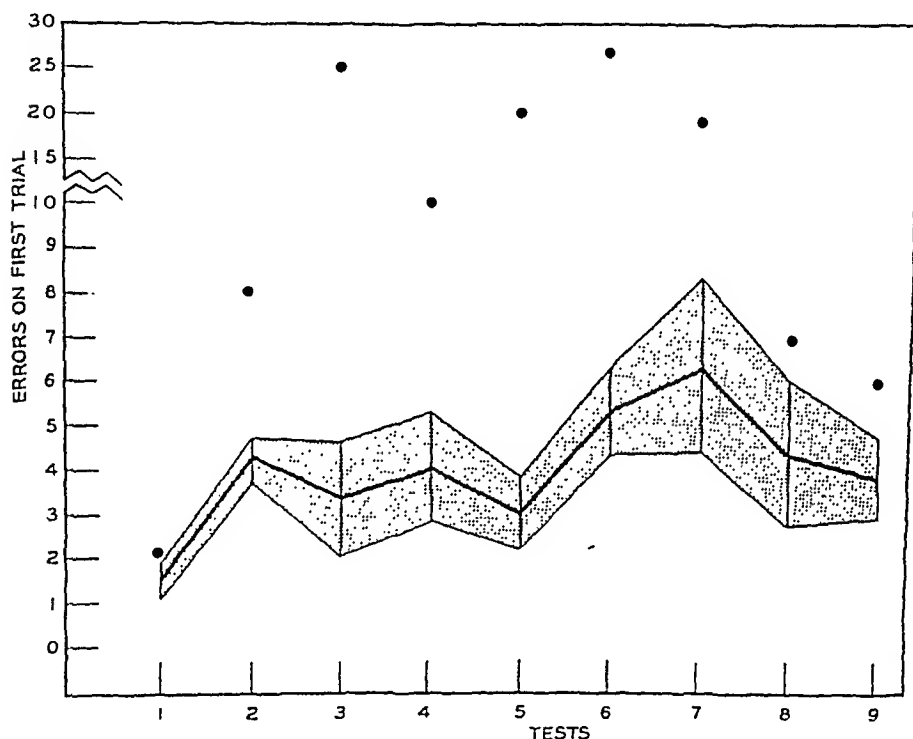


Fig. 7.—Graph indicating the performance of subject 22 (left occipital lobe completely removed), showing the number of errors (black dots) made on the first trial in each of the 9 tests. The profile in the lower portion of the figure represents normal variation in each test and is the same as that in figure 3.

aches and attacks of nausea, relieved by induced vomiting, during the past three years. Operation, performed on October 10 by Dr. Paul C. Bucy, involved complete extirpation of the right occipital lobe for removal of an oligodendroglioma. Recovery was uneventful, and the patient was discharged from the hospital on November 3. The preoperative intelligence quotient was 133 (standard-Binet L);

4. Halstead, W. C.; Walker, A. E., and Bucy, P. C.: Sparing and Nonsparing of Macular Vision Associated with Occipital Lobectomy in Man, *Arch. Ophth.* **24**:948-962 (Nov.) 1940.

the postoperative intelligence quotient was 133 (Stanford-Binet M). The patient was strongly "right handed." After her operation she resumed her secretarial duties in the office of a large corporation in Chicago. She was given additional responsibilities from time to time and an increase in salary. She is at present a student in a university.

It was possible to secure both preoperative and postoperative information in all 9 tests with subject 25. The two test periods were separated by an interim of six weeks. In figure 8 the preoperative results for this subject are plotted in solid dots and the postoperative results in hollow circles.

In the preoperative tests subject 25 grasped the instructions promptly and made only one error on test 1. She made 9 errors on test 2, as against an average of 4 errors for the average normal subject. She did not seem to be disturbed by her errors and worked steadily without seeking or receiving any assistance from the examiner. Her performance on test 3 fell within normal limits, and on test 4

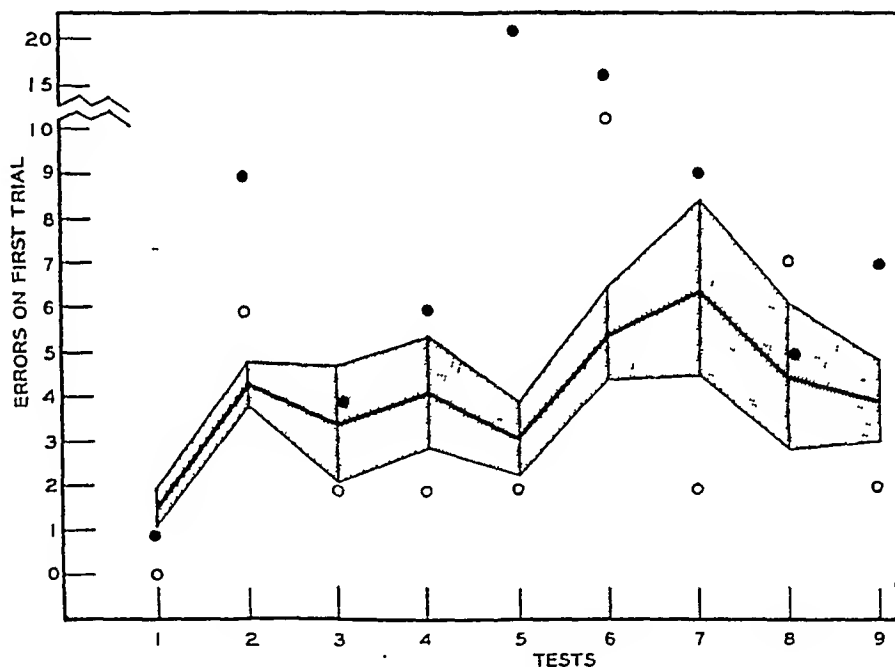


Fig. 8.—Graph indicating the preoperative (black dots) and postoperative (hollow circles) performance of subject 25 (right occipital lobe removed), showing the number of errors made on the first trial in each of the 9 tests. The profile in the lower portion of the figure represents the normal variation on each test and is the same as that in figure 3.

it was not notably different from the normal. She encountered considerable difficulty with tests 5 and 6 (quadrant), making 21 errors on the former and 16 errors on the latter. It is of interest that on the remaining tests, 7, 8 and 9, the performance of this subject was not notably differentiated from the average normal performance.

In the postoperative tests, with the exception of test 6 (quadrant), subject 25 encountered no particular difficulty, and in 6 of the 9 tests made fewer errors than the average normal subject. An analysis of various visual functions of subject 25 has been reported elsewhere.⁴

COMMENT

In the present investigation, we have been interested in the question whether certain forms of equivalence (in visually controlled responses) found in normal subjects likewise occur in persons with lesions of the brain. We were only incidentally concerned with determining the nature of the factors responsible for equivalence. Studies directed at the latter problem have been under way for some time in this laboratory. It seems clear that an adequate description of these factors for man requires intensive study of a wide range of behavioral functions in individual cases.⁵ Certain features of the present investigation bear directly on any preliminary interpretation of the variations from normal performance found in some of the patients with cerebral lesions and may be mentioned briefly.

1. *Visual Acuity for Form, Brightness and Color.*—Careful determinations of the visual acuity for form, brightness and color in all 6 of the experimental subjects have been made by the methods reported in connection with an analysis of the visual functions of subjects 22 and 25.⁴ No significant deviation from the normal was found in any of the 6 subjects with lesions of the brain which bore directly on their performances in the present investigation. The minimal visual form discrimination required in the test figures (which averaged approximately 3 by 3 degrees in size) subtended approximately 4 minutes of visual angle, a value well above the discrimination thresholds found for all 6 experimental subjects. Moreover, analysis of the errors made by the individual subjects indicates that relatively few errors were made on these particular figures.

2. *Visual Field Defect.*—Three of the 6 experimental subjects had a visual field defect associated with their cerebral lesion. Subjects 19 and 22 each had right homonymous hemianopia (with sparing of central vision) of *vue nulle* type.⁴ Subject 25 had left homonymous hemianopia (with splitting of central vision) of *vue nulle* type.⁴ It is of interest that of the 3 subjects with hemianopia, the performance of subject 19 was in general superior to that of any of the normal subjects (fig. 6). Likewise, the postoperative performance of subject 25 tended in general to equal or exceed the performance of the average normal subject. It thus seems improbable that the presence of hemianopia per se constituted the limiting factor in the performance of subject 22. This interpretation is further supported by an analysis of the errors made by this subject (fig. 7).

3. *Agnosia, Apraxia and Aphasia.*—Examinations of the language functions of all 6 experimental subjects have been made, including the

5. Klüver, H.: The Study of Personality and the Method of Equivalent and Non-Equivalent Stimuli, *Character & Personality* 5:91-112, 1936. Halstead.^{1b}

application of Head's tests and Halstead's test for aphasia, which covers twelve language functions, including agnosias and apraxias.⁶ In general, no evidence of disturbed language functions was obtained for any of the 6 experimental subjects which would throw light at this time on the deviations from normal performance obtained in the present investigation. Four of the 6 subjects (subjects 10, 19, 22 and 25) indicated a normal grasp of the verbal instructions, accurate perception of the test figures and the ability to make the required responses by equaling the average normal performance on test 1. Two of the 6 subjects (subjects 1 and 6) made 11 and 30 errors, respectively, on test 1, as compared with 1 or 2 errors made by the average normal subject. Nothing in the general behavior of these 2 subjects suggested failure to grasp the instructions. Both subjects began test 1 promptly and activated the response keys differentially after deliberate study of the test items in the viewing window. It was only after several consecutive errors that it became apparent to the experimenter that they had not grasped the specific point of test 1.

4. *Attitude and Persistence.*—All 6 of the experimental subjects evidenced an interested, "cooperative" attitude at the outset of the tests. Subjects 19, 22 and 25 worked readily and persistently throughout the 9 tests without requiring special motivation from the experimenter. Subjects 1, 6 and 10, on the other hand, exhibited signs relatively early in the tests that their willingness to continue was marginal indeed. It was this fact that led the experimenter to give them direct assistance. In the case of each of them, this "resistance" to the tests seemed to wax and wane as errors or correct responses were made. On reaching the end of test 6, each of them substantially refused to proceed further with the tests, an attitude which remains to the present. This is of particular interest in connection with Goldstein's⁷ description of the catastrophic reaction induced by certain test situations.

5. *Nature of the Tests.*—With the exception of subject 19, all of the experimental subjects had considerable difficulty with 1 or both of the quadrant tests (tests 5 and 6). It is of interest that the quadrant figures were the only test figures requiring a changing orientation to a vertical dimension of space. However, the performance of subject 1, for example, should be recalled in this connection: It was necessary for the experimenter to overcome an a priori conviction on the part of subject 1 that the quadrant test figures should be numbered from left to right rather than clockwise, as in the test.

6. Halstead, W. C.: A Test for Aphasia, to be published.

7. Goldstein, K.: Die Lokalisation in der Grosshirnrinde, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, pp. 600-842.

6. *Type of Lesion.*—Subjects 1, 6 and 10 had a primary lesion either of the right or of the left frontal lobe. These 3 subjects (*a*) deviated widely from the average normal person in the number of errors made on some of the tests, (*b*) required assistance and special motivation to complete most of the tests attempted and (*c*) refused to complete the series of tests beyond test 6. Subject 22, in whom the left occipital lobe had been removed, also deviated widely from the average normal performance in the number of errors made on most of the tests, but her general performance was not otherwise differentiated from that of the normal group. The performance of subject 19, who had a large lesion in the left parietotemporal region, was in general superior to that of the average normal subject. Likewise, the postoperative performance of subject 25, in whom the right occipital lobe had been removed, tended to equal or exceed the average normal performance.⁸

7. *Selection of Experimental Subjects.*—By restricting our consideration in the present report to the performances of subjects with lesions of the brain who have made good, or in some instances unusually good, postoperative social adjustments, we have incidentally selected those persons who are least differentiated from normal subjects in terms of their performances on the present group of tests. The fact that marked quantitative evidence of deviation from the normal is, nevertheless, apparent in our results is therefore of particular significance.

SUMMARY

Further analysis has been made of the grouping behavior of normal subjects and of persons with lesions of the brain from the series previously reported by one of us (W. C. H.). Groups of geometric test figures having certain characteristics in common were presented by means of a special apparatus. Both qualitative and quantitative evidences of deviation from normal performance were found in some of the experimental subjects. This evidence is in line with the earlier observations of Halstead obtained on these subjects. Various factors bearing on interpretation of the present results are discussed.

University Clinics, University of Chicago.

8. Jacobsen, C. F.; Elder, J. H., and Haslerud, G. M.: *Studies of Cerebral Function in Primates, Comparative Psychology Monographs*, Baltimore, Johns Hopkins Press, 1936, vol. 13, no. 3, p. 68. Lashley, K. S.: *Brain Mechanisms and Intelligence*, Chicago, University of Chicago Press, 1929.

CALCIFICATION OF THE CEREBRAL CORTEX ASSOCIATED WITH A MENINGOTHELI- OMATOUS MENINGIOMA

PATHOLOGIC STUDY, WITH COMMENT ON INCOMPLETE TYPES
OF THE NEUROCUTANEOUS SYNDROME

BEN W. LICHTENSTEIN, M.D.

AND

MAURICE LEV, M.D.

CHICAGO

Intracranial calcification is not rare, and it is associated with a variety of "physiologic" and pathologic conditions. Calcification of the pineal body or of the falx cerebri occurs with such frequency that the alteration is considered physiologic by many observers. The deposition of calcareous concretions in the region of the basal ganglia has recently been reviewed extensively by Eaton, Camp and Love.¹ Their report that the calcification occurs in and about the finer cerebral blood vessels coincides with our observations in cases of a similar condition. This study, on the other hand, pertains to calcification of the brain parenchyma itself, particularly the cortex. Calcification of the cortex of the brain takes place in a variety of pathologic states, the most common being tuberous sclerosis, in which the alterations may be noted within some of the tuberosclerotic nodules. According to Yakovlev and Corwin,² the calcification in such lesions tends to occur not in the center of the nodule but in the periphery of the subcortical softening, facing the white matter, that is, under the cortex in the depth of the convolutions. In a closely related pathologic state, however, namely, the glial nodules of the cortex associated with Recklinghausen's disease, we have observed the calcareous concretions within the glial-sclerotic nodule itself.

The type of calcification in the cerebral cortex we are describing in this contribution has been reported and verified histologically, to our

From the Illinois Neuropsychiatric Institute; the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, and the Chicago State Hospital.

1. Eaton, L. M.; Camp, J. D., and Love, J. G.: Symmetric Cerebral Calcification, Particularly of the Basal Ganglia, Demonstrable Roentgenographically, *Arch. Neurol. & Psychiat.* **41**:921 (May) 1939.

2. Yakovlev, P. I., and Corwin, W.: A Roentgenographic Sign in Cases of Tuberous Sclerosis of Brain (Multiple "Brain Stones"), *Arch. Neurol. & Psychiat.* **42**:1030 (Dec.) 1939.

knowledge, only twice before. In both instances this alteration occurred in association with cutaneous (facial) and leptomeningeal angiomatoses. Our paper is the first in which the cortical calcification has been reported in association with a meningotheliomatous meningioma. The close genetic relationship between angioma and meningothelioma will be pointed out later, and the pleomorphic variety of incomplete or atypical forms of the neurocutaneous syndrome, of which we believe our case is an example, will be discussed.

REPORT OF A CASE

History.—Mrs. M. Z., a white woman aged 53, was admitted to the Chicago State Hospital on May 21, 1941. The onset of her illness was eighteen months before, when she began to complain of failing vision. Soon afterward, she became nervous and frightened and stayed home a great deal. She was taken to an ophthalmologist, who reported that her right eye was totally blind and that vision in her left eye was reduced to counting fingers at a distance of 8 feet (245 cm.). The left pupil reacted sluggishly to light, and the right pupil did not react at all. Examination of the optic fundi revealed bilateral advanced primary optic nerve atrophy. The Wassermann reaction of the blood was negative, and roentgenograms of the skull showed no abnormalities. The pathogenesis of the primary optic nerve atrophy could not be determined. A short time afterward she was in an automobile accident, in which she sustained minor bruises. After this incident her nervousness increased and she became confused and agitated. She imagined she was not at home and demanded that she be taken home. She imagined seeing dogs and little children, to whom she talked. She became very jealous of her husband, pulled his hair, scratched his face and called him vile names. As her mental condition became progressively worse, she was admitted to the Cook County Psychopathic Hospital on May 18, 1941 and shortly thereafter was transferred to the Chicago State Hospital, with a diagnosis of presenile dementia.

Physical Examination.—Inspection revealed her to be well nourished. The heart was enlarged to the left, and a soft systolic murmur was heard at the apex. The blood pressure was 150 systolic and 90 diastolic. The olfactory sense was not tested. With the exception of advanced bilateral primary optic nerve atrophy, no abnormalities were found in the neurologic examination.

Laboratory Data.—The blood count revealed 4,500,000 red cells per cubic millimeter, 14.5 Gm. of hemoglobin per hundred cubic centimeters and 5,200 white cells per cubic millimeter. The Kahn reaction of the blood was negative. The Pandy reaction of the cerebrospinal fluid was faintly positive; the Lange colloidal gold curve was 0000000000. The sugar content of the cerebrospinal fluid was 74 mg. per hundred cubic centimeters.

Mental Examination.—After admission to the hospital the patient was quiet and cooperative. She appeared apathetic and was grossly disoriented, and there was no play of emotions on her face as she spoke. When asked about her vision she said, "I can't be blind; I see everything." On questioning, however, it was apparent that she could not count fingers at a distance of 3 feet (90 cm.). The first clinical impression was that of organic disease of the brain, undetermined of type.

On June 9 an electroencephalographic study was made by Dr. Chester W. Darrow, of the psychophysiology laboratory of the Illinois Institute for Juvenile

Research. He reported that the patient was quiet and cooperative throughout the examination. The record showed a large amount of 2 to 3 per second waves of large potential arising from the frontal and the motor regions. He expressed the opinion that the tracings from all areas were suggestive of degenerative changes in the brain. On June 11 pneumoencephalographic examination revealed moderate diffuse internal hydrocephalus of the lateral and third ventricles.

Clinical Diagnosis.—In view of the clinical history and course, the degenerative changes evidenced by the brain waves and the moderate and symmetric internal hydrocephalus, the majority opinion of the staff members was that the patient was suffering from a form of presenile dementia, probably Alzheimer's disease. The primary optic nerve atrophy, however, remained unexplained.

Course.—The patient's mental condition continued to be poor; bronchopneumonia developed, and she died on Nov. 3, 1941.

Anatomic Diagnosis.—The diagnosis was meningotheiomatic meningioma arising from the leptomeninx in the vicinity of the olfactory tracts; Alzheimer's disease; focal and confluent bronchopneumonia, and calcification of the cerebral cortex of the convolutions adjacent to the meningioma.

Gross Pathologic Observations.—The brain was removed and hardened in a dilute concentration of solution of formaldehyde U. S. P. (1:10). The leptomeninges were everywhere thin and transparent. The blood vessels at the base of the brain contained single sclerotic plaques. On the orbital surface of the frontal lobe, just in front of the hypophysis, was a round, disk-shaped tumor 4 cm. in thickness. This tumor compressed both olfactory tracts, both optic nerves and the optic chiasm. It was firmly adherent to the roof of both orbits, into which it had grown. After fixation, the brain was cut in a midsagittal plane. That portion of the tumor which bordered on the parenchyma of the brain was soft and grayish white and measured up to 10 mm. in thickness. This soft tissue merged rather sharply into the sclerotic portion of the tumor that had grown into the roof of both orbits. On section of the brain, the lateral and third ventricles were observed to be moderately dilated. The cortex and the basal ganglia were dark gray brown. When the orbital gyri were sectioned, the knife encountered calcific material.

Microscopic Pathologic Observations.—Tumor: The soft portion of the tumor showed the typical histologic picture of a meningotheiomatic meningioma (fig. 1). It was composed of alveoli of mesothelial cells of uniform appearance. The alveoli were separated by interlacing bundles of collagenous connective tissue, which stained deep red with Van Gieson's method. This portion merged rather sharply into the sclerotic portion, in which islands of tumor tissue were separated by trabeculae of bone (fig. 2).

Brain: The leptomeninges were thin and free from cellular infiltrations. The cytoarchitecture was, on the whole, well preserved. Here and there throughout the cortex, clear areas devoid of cellular elements were seen, and in many areas the ganglion cells appeared pale and shrunken. In the deeper layers of the cortex a moderate degree of satellitosis was observed. The calcific material described in the gross specimen took the dyes rather deeply. The largest concretions were seen in the center of the affected area (fig. 3). Here the concretions were round and the internal lamination was distinct. In adjacent areas, structures identical with the corpora arenacea, or the so-called brain sand granules, commonly seen in the pineal body were observed. In the periphery of the affected zone, spherical, centrally laminated concretions no larger than the nuclei of ganglion cells were

arranged in nests. The concretions which were most recently precipitated were not laminated but were rather amorphous and granular. Many of the concretions had fallen out, leaving clear areas. There was no increase in glia about the

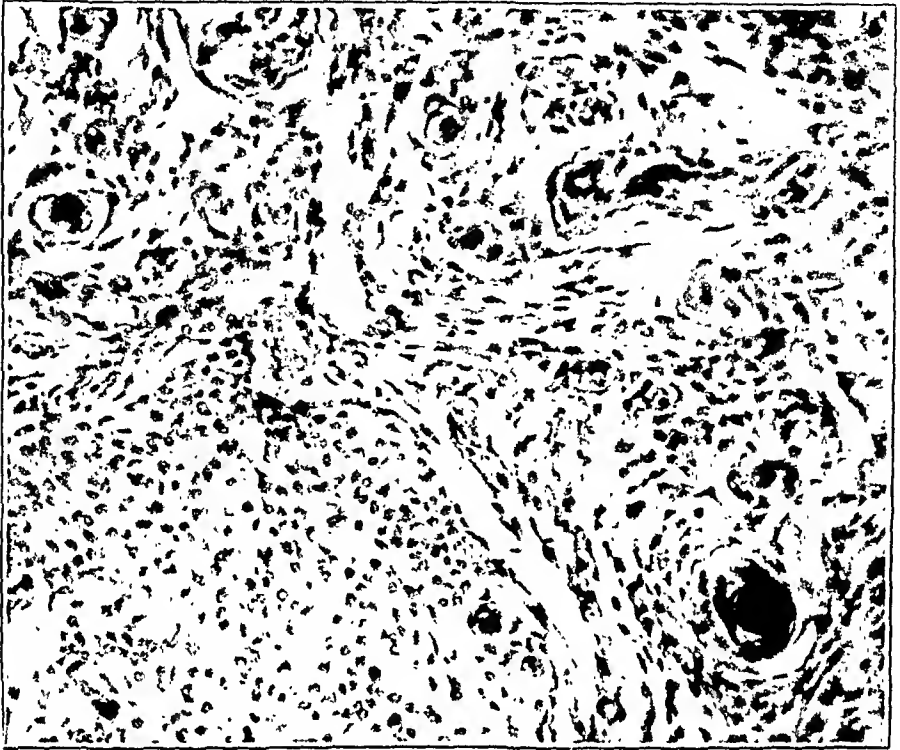


Fig. 1.—Low power photomicrograph of a portion of the tumor, showing the whorls characteristic of a meningotheliomatous meningioma. Iron hematoxylin stain.

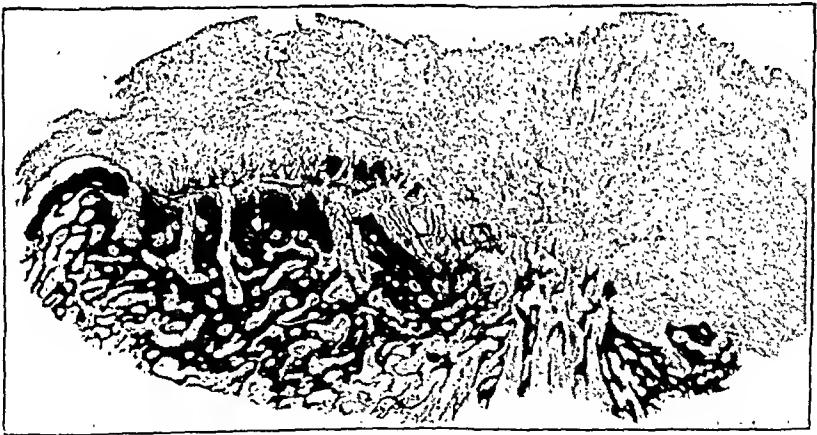


Fig. 2.—Low power photomicrograph of the meningioma. The deeply stained tissue in the lower part of the tumor is trabeculae of bone. Van Gieson stain.

concretions. In Bielschowsky preparations the concretions were surrounded by clear areas devoid of neurofibrils (fig. 4 *B*). More striking, however, were the large numbers of senile plaques scattered throughout all portions of the cortex

of the brain. Ganglion cells showing the condensed and spiral neurofibrillary apparatus characteristic of Alzheimer's disease were seen in large numbers in all fields (fig. 4A).

CLINICAL CONSIDERATIONS

The clinical diagnosis of Alzheimer's disease, corroborated by electroencephalographic evidence of degeneration of the nervous system and pneumoencephalographic evidence of atrophy of the cortex of the brain, was verified by the microscopic examination. The bilateral primary optic nerve atrophy, however, which resulted from the pressure of the meningioma on the optic nerves and the optic chiasm, was a disturbing clinical observation. A stereoscopic examination of the lateral roentgenograms of the skull taken at the time the encephalogram was obtained showed a faintly outlined but rather distinct shadow just above the orbits in the

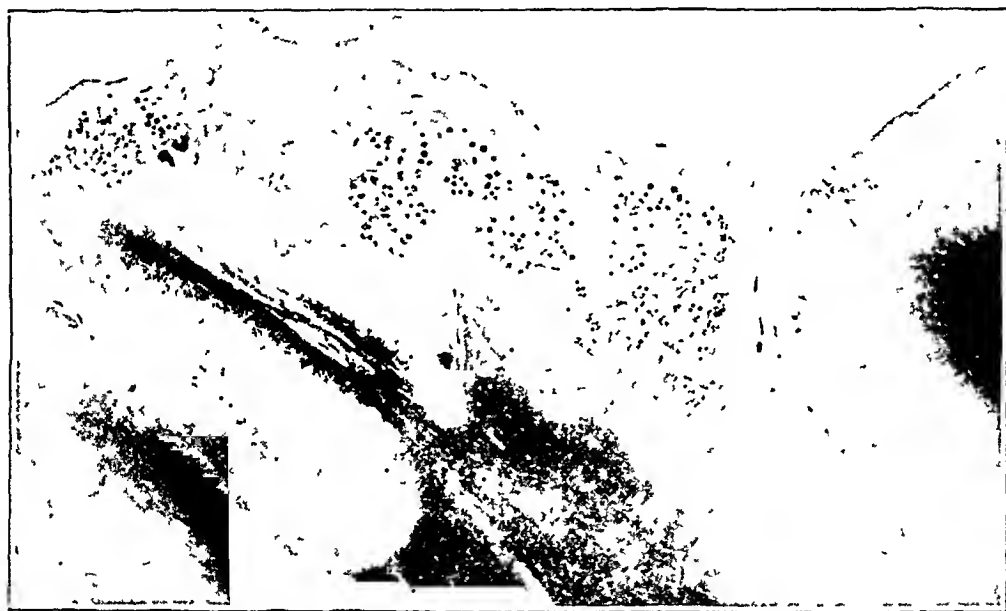


Fig. 3.—Low power photomicrograph through the orbital gyrus, showing the intracortical concretions. Weil stain.

region where the sclerotic portion of the meningioma was seen. The calcification in the brain substance itself could not be detected in the roentgenograms. It is unfortunate that the olfactory sense was not examined, since anosmia coupled with primary optic nerve atrophy might have suggested the possibility of a basofrontal lesion just in front of the optic chiasm.

PATHOLOGIC CONSIDERATIONS

From the histologic study of the case reported it is evident that one is dealing with a meningotheiomatous meningioma associated with intracortical calcifications in the adjacent convolutions. Both conditions were present in a brain showing histologic evidence of Alzheimer's disease.

We believe that it will be the consensus that the Alzheimer disease was not pathogenetically related to the other two states. Many investigators may contend that the meningothelioma, too, was wholly unrelated to the



Fig. 4.—*A*, high power photomicrograph of a section through the cerebral cortex, showing the Alzheimer changes in the ganglion cells.

B, low power photomicrograph of a section through the cortex, showing the concretions surrounded by clear areas devoid of neurites. Bielschowsky stain.

intracortical calcifications, but we shall attempt to show that the coexistence of the latter two pathologic states was not accidental.

The medical literature is replete with instances in which cutaneous anomalies have been associated with neurologic disorders. The two outstanding disorders belonging to this group are Recklinghausen's disease and tuberous sclerosis. To them is added von Hippel-Lindau disease, in which the external evidence of disorder is present not in the skin but in the eye. Of these three disorders atypical (incomplete, central or latent) varieties occur in which external evidences are lacking despite the involvement of the nervous system.

In addition to these three major types of the so-called neurocutaneous syndrome, many minor ones occur, among them being Sturge-Weber disease. The pathologic syndrome we are describing is closely related to the latter disorder.

The combination of a vascular nevus in the trigeminal region with telangiectasis of the pia mater and angiomas of the brain was first described clinically by Sturge³ in 1879. Kalischer,⁴ in 1897, described the anatomic changes in a case of this condition. Weber,⁵ first in 1922 and later in 1929, described the roentgenographic alterations in the brain of a patient presenting a vascular nevus of the face with contralateral hemiplegia. In his 1929 publication, the sinuous calcified shadow corresponding to the surface of the brain was clearly seen. Dimitri,⁶ in 1923, published the report of a case in which an angioma of the brain produced a distinct shadow in the roentgenogram, and Marque,⁷ in 1927, described 2 cases with similar roentgenographic changes. Because of the presence of the vascular nevus on the face, the calcifications seen in the roentgenograms were interpreted as calcified angiomas.

Krabbe,⁸ in 1934, published the anatomic observations in the case of a white youth aged 19 years who since birth had had a large vascular

3. Sturge, A.: A Case of Partial Epilepsy, Apparently Due to a Lesion of One of the Vaso-Motor Centers of the Brain, *Tr. Clin. Soc., London* **12**:162, 1879.

4. Kalischer, S.: Demonstration des Gehirns eines Kindes mit Telangiectasie der linksseitigen Gesichtskopfhaut und Hirnoberfläche, *Berl. klin. Wchnschr.* **33**: 1059, 1897.

5. Weber, F. P.: Right-Sided Hemi-Hypotrophy Resulting from Right-Sided Congenital Spastic Hemiplegia, with a Morbid Condition of the Left Side of the Brain Revealed by Radiograms, *J. Neurol. & Psychopath.* **3**:134, 1922; A Note on the Association of Extensive Hemangiomatous Naevus of the Skin with Cerebral (Meningeal) Haemangioma, Especially Cases of Facial Vascular Naevus with Contralateral Hemiplegia, *Proc. Roy. Soc. Med. (Sect. Neurol.)* **22**:431, 1929.

6. Dimitri, J.: *Rev. Asoc. méd. argent.* **36**:1029, 1923.

7. Marque, A.: Consideraciones sobre angiomas en la infancia, *Rev. oto-neuro-oftal.* **1**:202, 1927; cited by Krabbe.⁸

8. Krabbe, K. H.: Facial and Meningeal Angiomatosis Associated with Calcifications of the Brain Cortex, *Arch. Neurol. & Psychiat.* **32**:737 (Oct.) 1934.

nevus over the right side of his face. Roentgenograms of the skull showed an irregular shadow in the right occipital lobe corresponding to the cerebral gyri, with darker lines corresponding to the sulci. Some of the darker lines had double contours. The patient had been subject to epileptiform seizures for several years, and death followed several attacks. Histologic examination of the brain showed that the shadow seen in the roentgenogram was due to calcification of the outer layers of the cortex, and not of the pia mater or the blood vessels in its vicinity. The calcification consisted of small granules of lime salts localized in the second and third layers of the cortex. The pia mater over the calcified area was abundantly vascularized, but no true angioma was seen.

Intracortical calcification, as seen in our case and in the case reported by Krabbe, was seemingly first reported by Volland⁹ in 1913, whose case was clinically and pathologically similar to Krabbe's. Volland's patient, a boy, had suffered from epileptiform attacks, and his mental development had been slow. There was a vascular nevus on the left side of his face, and he had contralateral hemiplegia. Autopsy revealed that the left cerebral hemisphere was smaller than the right. The pia mater over the left side of the brain, particularly in the region of the frontal bone over the base of the third frontal convolution, over the tip of the temporal lobe and over the left cuneus, was greatly thickened and was rich in blood vessels. Microscopically, the leptomeninges were seen to be the seat of angiomatous formations. In the sclerotic areas of the brain, particularly in the left occipital lobe, but also to a less degree in the left frontal lobe and in the cornu ammonis, the cortex, and to a lesser degree the subcortical white substance, was the seat of many calcareous concretions.

The calcification in Volland's case was much more extensive than in either Krabbe's case or the one described in this report. Volland's case and that of Krabbe were similar in that the intracerebral calcifications were associated with leptomeningeal angiomatoses and cutaneous vascular nevi. Our case differed from theirs in two ways—first, no cutaneous lesion was present, and, second, instead of an angiomatous meningioma of the leptomeninx, a meningotheliomatous meningioma was present. On analysis, one sees that these differences are minor and that our case belongs to the same group as theirs. The absence of cutaneous manifestations in any case of the neurocutaneous syndrome (Recklinghausen's disease or tuberous sclerosis) is not rare, and in such instances the condition is usually designated as incomplete, central, abortive or latent. More common than the abortive peripheral type is

9. Volland: Ueber zwei Fälle von zerebralem Angioma nebst Bemerkungen über Hirnangiome, Ztschr. f. d. Erforsch. u. Behandl. d. jugendl. Schwachsinn 6:130, 1913.

the abortive or incomplete central type, in which cutaneous manifestations are present without changes in the meninges or the central nervous system. Examples of this type are the vascular nevi of the face unassociated with meningeal or cerebral alterations. In some instances a mixed type of the neurocutaneous syndrome occurs, as in the case reported by Grieg,¹⁰ in which adenoma sebaceum of the face (Pringle's disease), which is usually observed in association with tuberous sclerosis, accompanied a meningeal nevus.

The differences between an angiomatous meningioma, such as the tumor in the cases of Volland and Krabbe and a meningotheliomatous meningioma, such as the tumor in our case, are minor. The primitive leptomeninx, regardless of the fact that it may originate from the neural crest and is, therefore, ectodermal in origin, according to the observations of Harvey and Burr,¹¹ is histopathologically mesenchymal in character. The early mesenchyma may be considered to be the parent organ of two types of tissue—the nutritive (blood vessels) and the supportive. The angiomatous meningioma is basically a growth of the nutritive (vascular) component of the primitive leptomeninx, and the meningotheliomatous meningioma is essentially the most common type of growth arising from the supportive component of the primitive leptomeninx. According to Bailey and Bucy,¹² at least nine varieties of meningeal tumors have been differentiated, and it is our belief that in the future varieties other than angioma and meningothelioma will be observed in association with cerebral calcification.

Terminology has always been a difficult part of clinical medicine, especially when one is dealing with incomplete, poorly recognized or little known diseases.

Krabbe,⁸ in his contribution on facial and meningeal angiomatoses associated with calcification of the cerebral cortex, closed with the sentence, "If this disease, forming an entity, should deserve a name, it might well be Parkes Weber-Dimitri's disease." Weber⁵ (August 1922) and Dimitri⁶ (1923) were the first, it will be recalled, to record the characteristic roentgenographic changes, which Krabbe showed were due to intracerebral calcification rather than to calcified blood vessels. Since Krabbe⁸ (1934) was the first to demonstrate that the sinuous shadows seen in the roentgenogram were indicative of calcification in the cortex

10. Grieg, D. M.: A Case of Meningeal Naevus Associated with Adenoma Sebaceum, *Edinburgh M. J.* **28**:105, 1922.

11. Harvey, S. C., and Burr, H. S.: The Development of the Meninges, *Arch. Neurol. & Psychiat.* **15**:545 (May) 1926. Harvey, S. C.; Burr, H. S., and Van Campenhout, E.: Development of Meninges, *ibid.* **29**:683 (April) 1933.

12. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, *Am. J. Cancer* **15**:15, 1931.

of the brain, many authors (Moniz and Lima¹³) have alluded to the disorder as Krabbe's disease. It was Volland⁹ (1913), however, who first showed that the calcifications noted in the brain of a boy with a facial vascular nevus were in the brain substance itself and not in the blood vessels. Since Sturge³ was apparently the first to describe the neurocutaneous syndrome clinically, the association of vascular nevi of the face, particularly in the region of distribution of the trigeminal nerve, with the characteristic roentgenographic shadows, first described by Weber,⁵ is now termed the Sturge-Weber syndrome.

The association of epilepsy with progressive facial hemiatrophy has been noted by many observers. Merritt, Faber and Bruch¹⁴ called attention to the presence of sinuous shadows in the roentgenograms of the skull of patients with progressive facial hemiatrophy. These shadows closely conform to what has been described in the past as indicative of calcified angioma (Weber and Dimitri), but which Krabbe showed to be intracortical, nonvascular calcifications. The cause of progressive facial hemiatrophy is indefinite. According to some authors, the disorder is the manifestation of a form of scleroderma. A striking histopathologic alteration in cases of scleroderma is the diffuse increase in the connective tissue. This growth of connective tissue—rich in collagen—constricts the nutrient blood vessels, and atrophy of the affected tissues may result. It is important to remember that hemangiomas, too, undergo sclerosis. This process, which is much more pronounced in some cases than in others, is also characterized by an overgrowth of collagenous connective tissue, which finally obliterates the blood vessels. Thus, in cases both of hemangioma (to which the vascular nevus belongs) and of progressive facial hemiatrophy, a diffuse overgrowth of connective tissue may occur. Both conditions, too, may be associated with epilepsy and Dimitri-Weber cerebral calcifications. In many instances of vascular nevi of the face the angiomatous process involves the subcutaneous tissue, the muscles, the fasciae and the skull itself. Similarly, in cases of progressive facial hemiatrophy the atrophic-sclerotic process may involve the skin, the subcutaneous fat, the connective tissue, the muscles and the bones. The association of pigmentary with vascular nevi is well known, and the occurrence of pigmentary nevi with progressive facial hemiatrophy has also been observed.

Geyelin and Penfield,¹⁵ reported the clinical and roentgenographic observations in cases of a "peculiar type of epilepsy" that appeared in

13. Moniz, E., and Lima, A.: Pseudo-angiomes calcifiés du cerveau, angiome de la face et calcifications corticales du cerveau (maladie de Knud H. Krabbe), *Rev. neurol.* **63**:743, 1935.

14. Merritt, K. K.; Faber, H. K., and Bruch, H.: Progressive Facial Hemiatrophy, *J. Pediat.* **10**:374, 1937.

15. Geyelin, H. R., and Penfield, W.: Cerebral Calcification Epilepsy, *Arch. Neurol. & Psychiat.* **21**:1020 (May) 1929.

one family, including the father and all 4 children. Roentgenograms in 4 of the cases showed distinct calcified areas in the brain substance. In many instances the shadows appeared circular or tubular, with furrows that seemed to follow the fissures of the brain. Many of these shadows were identical with those described by Weber and Dimitri. In 1 instance craniotomy was performed, which revealed the calcified areas to be harder than normal and the overlying leptomeninges less vascular than usual. Microscopic examination revealed that the calcification "began in the deeper layers of the gray matter and extended into the white matter." In the center of the calcified zone were loosely arranged fibrous neuroglia cells and many scattered calcified granules, the size of which varied from less than the diameter of the nucleus of a nerve cell to the size of a Betz cell. "The small capillaries stood out and seemed to be numerous but were frequently converted into calcified tubes."

According to Geyelin and Penfield, the primary change in their case was a local vascular one. Obliteration had taken place in the small vessels, which resulted in local destruction of cerebral tissue, and the calcification was secondary to this local destruction. They stated that the process might be called "obliterating endarteritis of the cerebral hemispheres."

It is difficult to decide whether the calcification described by Geyelin and Penfield is of the Weber-Dimitri type. In the cases of Volland and Krabbe and in our case the blood vessels were not calcified. In the case of Geyelin and Penfield, however, the calcification was not restricted to the blood vessels but was loose in the parenchyma as well.

We do not believe that it is germane to this contribution to discuss the chemical nature of the concretions which have been so loosely referred to as calcium. Suffice it to say that debate has arisen as to the exact chemical nature of the deposits.

It should be emphasized that angiomas of the brain do undergo calcification, but the roentgenographic changes are not similar to those seen with the type of calcification described in this report.

SUMMARY AND CONCLUSIONS

The clinical and pathologic features of a case of Alzheimer's disease complicated by the presence of a large meningioma of the olfactory groove are presented.

The suggestion is made that the association of calcification of the cerebral cortex with the meningiothelioma is part of a pathologic complex and not a mere coincidence.

The association of the Dimitri-Weber calcifications in the brain with pathologic conditions other than vascular nevi in the region of distribution of the trigeminal nerve (Sturge-Weber syndrome) is reviewed.

NEUROGENIC HYPERTHERMIA AND ITS TREATMENT WITH SOLUBLE PENTOBARBITAL IN THE MONKEY

CAPTAIN L. E. BEATON*

MEDICAL CORPS, ARMY OF THE UNITED STATES
AND

C. LEININGER, M.S.

W. A. MCKINLEY, B.A.

H. W. MAGOUN, PH.D.
AND

S. W. RANSON, M.D.†
CHICAGO

Within recent years an increasing number of papers have appeared on neurogenic hyperthermia, a severe and occasionally fatal elevation of body temperature which sometimes results from acute injury to the brain, especially if the hypothalamic region has been involved (Cushing,¹ Gagel,² Alpers,³ Dott,⁴ Erickson,⁵ Davison⁶ and Zimmerman⁷). This acute hyperthermia, which Cushing¹ characterized as a *bête noire*

* At the time this study was made Dr. Beaton was Medical Fellow of the National Research Council.

† Dr. Ranson died Aug. 30, 1942.

From the Institute of Neurology, Northwestern University Medical School.

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1. Cushing, H.: *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. Gagel, O.: *Symptomatologie der Erkrankungen des Hypothalamus*, in Bumke, O., and Foerster, O.: *Handbuch der Neurologie*, Berlin, Julius Springer, 1936, vol. 5, pp. 482-522.

3. Alpers, B. J.: Hyperthermia Due to Lesions in the Hypothalamus, *Arch. Neurol. & Psychiat.* **35**:30-42 (Jan.) 1936.

4. Dott, N. M.: *Surgical Aspects of the Hypothalamus*, in Clark, W. E. LeG.; Beattie, J.; Riddoch, G., and Dott, N. M.: *The Hypothalamus*, London, Oliver & Boyd, 1938, pp. 131-185.

5. Erickson, T. C.: Neurogenic Hyperthermia (A Clinical Syndrome and Its Treatment), *Brain* **62**:172-190, 1939.

6. Davison, C.: Disturbances of Temperature Regulation in Man, *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:774-823, 1940.

7. Zimmerman, H. M.: Temperature Disturbances and the Hypothalamus, *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:824-840, 1940.

of the neurosurgeon, has been ascribed to a dysfunction of the hypothalamic temperature-regulating mechanism, and a variety of antipyretic agents have been utilized in attempts to control it, but without success. In 1938, Dott⁴ wrote:

We know of no pharmacological substance which will effectively lower the raised temperature in cerebrogenic hyperthermia. Artificial cooling is our only effective treatment.

It appeared that if acute hyperthermia could be produced with some regularity by hypothalamic injury in experimental animals, an opportunity would be afforded for a study of the treatment of this disorder. In 1935 Ranson and Ingram⁸ reported cases of postoperative elevation of body temperature following injury to the anterior portion of the hypothalamus in a series of monkeys operated on under anesthesia induced with soluble pentobarbital U. S. P. (pentobarbital sodium). It was noted that the hyperthermia did not commence until some hours after operation, when the animals had recovered from the anesthetic, and this suggested that pentobarbital might be an effective therapeutic agent for hyperthermia. By 1938 investigation of the temperature-regulating mechanisms in the hypothalamus had progressed to the extent that it was possible to report the results of a series of controlled experiments in which lesions in the anterior portion of the hypothalamus of cats, operated on under ether, resulted in postoperative hyperthermia, which was reduced by the injection of soluble pentobarbital (Ranson and Clark⁹). It was stated⁹:

The possibility that this drug [nembutal] might be useful in combating neurogenic hyperthermia in man should receive the consideration of neurosurgeons.

The clinical importance of the observation appeared to warrant further study, and the following report is concerned with the results of additional investigation of experimental hyperthermia and its treatment with pentobarbital in a series of monkeys.

METHOD

With use of the Horsley-Clarke technic (Ranson¹⁰), and with full aseptic precautions, bilateral electrolytic lesions were placed in the hypothalamic region of monkeys under ether anesthesia. After operation, the animals were confined in a hammock in a room at or a little above 80 F. A continuous record of their rectal temperature was obtained with a Leeds and Northrup micromax, and they were observed at frequent intervals over a period of twenty-four to forty-

8. Ranson, S. W., and Ingram, W. R.: Hypothalamus and Regulation of Body Temperature, *Proc. Soc. Exper. Biol. & Med.* **32**:1439-1441, 1935.

9. Ranson, S. W., and Clark, G.: Neurogenic Fever Reduced by Nembutal, *Proc. Soc. Exper. Biol. & Med.* **39**:453-455, 1938.

10. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotaxic Instrument, *Psychiat. en neurol. bl.* **38**:534-543, 1934.

eight hours. In each case the body temperature fell after the induction of anesthesia, and while the animal was being prepared for operation. During the operation external heat was applied, and in many instances the temperature rose. The anesthetic and the external heat were discontinued at the end of the operation, but the block marked *ANES* in the temperature charts includes the time required for recovery. The body temperature before and during the operation was influenced by the anesthetic and by the application of external heat, and only those changes which occurred after the termination of the operation can be regarded as significant.

Tests of temperature regulation in the chronic state were made by placing the animal in an ice box at 32 F. or by confining it in a hotbox at 122 F. The monkey's head and hands protruded from the hotbox so that observations could be made on sweating and respiration. Preoperative tests made on each animal served for comparison. At autopsy the location and extent of the lesions were verified by microscopic examination of serial sections through the hypothalamic region of the brain.

TEMPERATURE REGULATION IN THE ACUTE STATE

Control Experiments.—The disorders in temperature regulation to be described can best be appreciated against a background furnished by the acute postoperative course of 3 monkeys subjected to the same anesthetic and operative procedure, but in which the lesions were not in a position to affect the hypothalamic temperature-regulating mechanisms. The location of the lesions in these control animals was anterior (monkey 1, fig. 1), dorsal (monkey 2, fig. 2) and lateral (monkey 3, fig. 3) respectively to the preoptic region and the anterior portion of the hypothalamus. When placed in a room at 80 F. or above after operation, the animals either maintained their body temperature within the normal range of 100 to 102 F. from the start (monkey 3, fig. 3) or did so after a transient fall to 97.6 F. (monkey 1, fig. 1) or 98.6 F. (monkey 2, fig. 2). They subsequently exhibited normal temperature regulation throughout the period of survival.

Fatal Hyperthermia.—In striking contrast to the controls, 9 other monkeys, in which symmetric bilateral lesions were produced within the preoptic region or the anterior portion of the hypothalamus, exhibited severe, acute postoperative hyperthermia. In 2 animals of this group the hyperthermia was allowed to proceed without treatment, and the observations on these animals may first be presented.

In monkey 4 the large bilateral lesion of the preoptic region shown in figure 4 *B* was produced. The postoperative course is illustrated in figure 4 *A*. The animal's temperature was maintained between 101 and 101.5 F. during the operation. One-half hour after operation, when the animal appeared to have fully awakened from the anesthesia, its temperature began to rise in almost a linear fashion and reached a peak of 109.1 F. five hours after operation. The animal then became comatose; its temperature fell gradually to 108 F., then rapidly to 106.5 F., and it died. The heart rate, which remained between 200 and 230 per

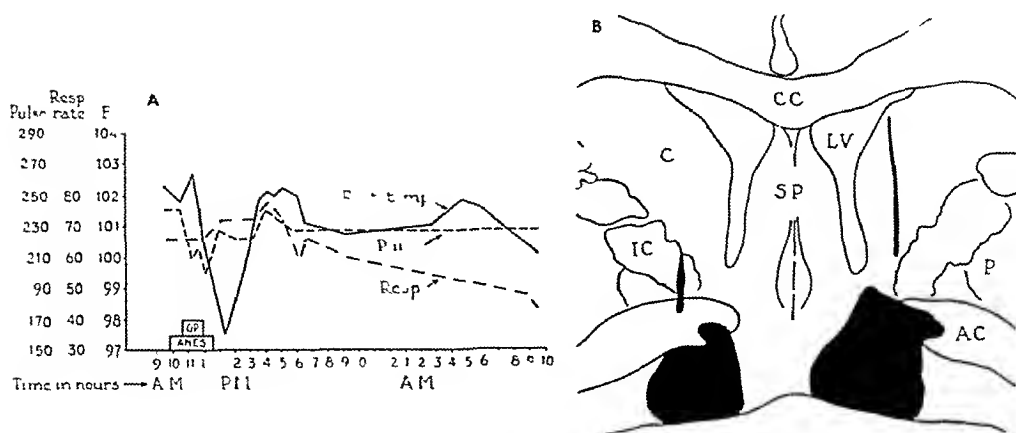


Fig. 1 (monkey 1).—*A*, temperature chart; *B*, lesions in the brain.

In this figure and in the accompanying figures, the following abbreviations are used: *AC*, anterior commissure; *BP*, basis pedunculi; *C*, caudate nucleus; *CC*, corpus callosum; *F*, fornix; *GP*, globus pallidus; *IC*, internal capsule; *LV*, lateral ventricle; *MB*, mamillary body; *MI*, massa intermedia; *NR*, red nucleus; *OC*, optic chiasm; *OT*, optic tract; *P*, putamen; *SP*, septum pellucidum; *VA*, nucleus ventralis anterior, and *III*, third ventricle.

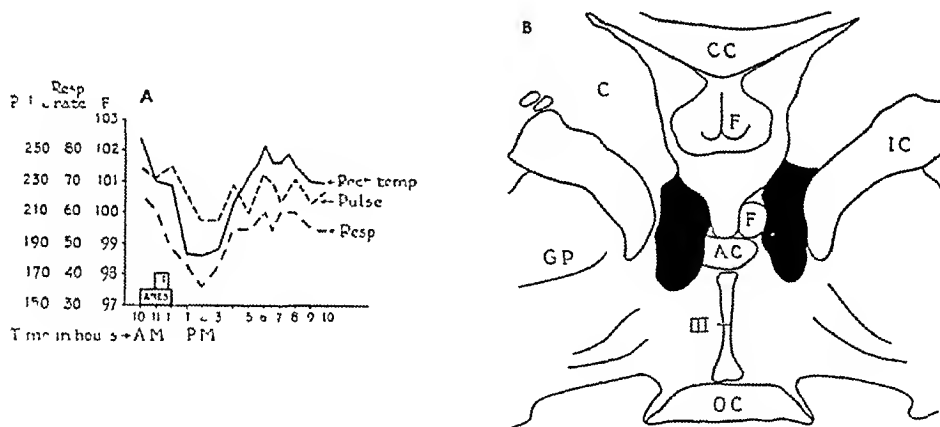


Fig. 2 (monkey 2).—*A*, temperature chart; *B*, lesions in the brain.

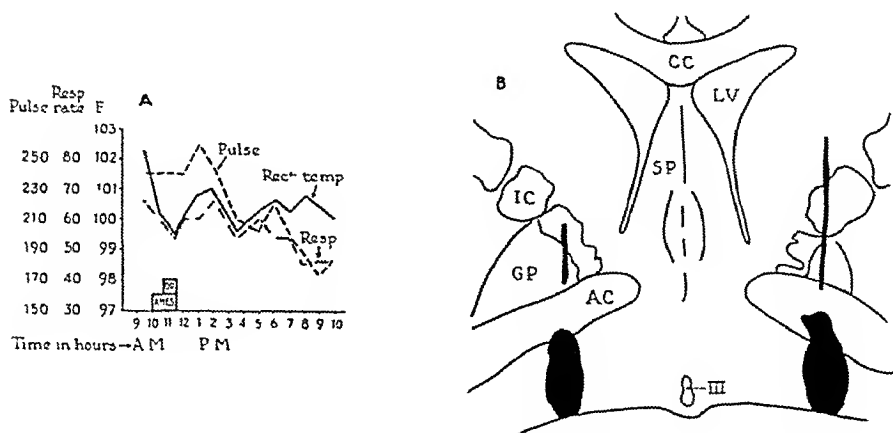


Fig. 3 (monkey 3).—*A*, temperature chart; *B*, lesions in the brain.

minute during the course of the operation and immediately thereafter, became elevated with the rise in temperature and reached a peak of 360 per minute just before death. The respiratory rate, which was between 50 and 65 per minute during the operative period, rose only slightly during the period of hyperthermia, to between 65 and 80 per minute. With a rectal temperature of 108 F. the animal exhibited some shivering, and at 109 F. piloerection occurred. Though the trunk was warm and some rubor of the chest was observed, the extremities remained cold, and at no time during the hyperthermia did the animal sweat.

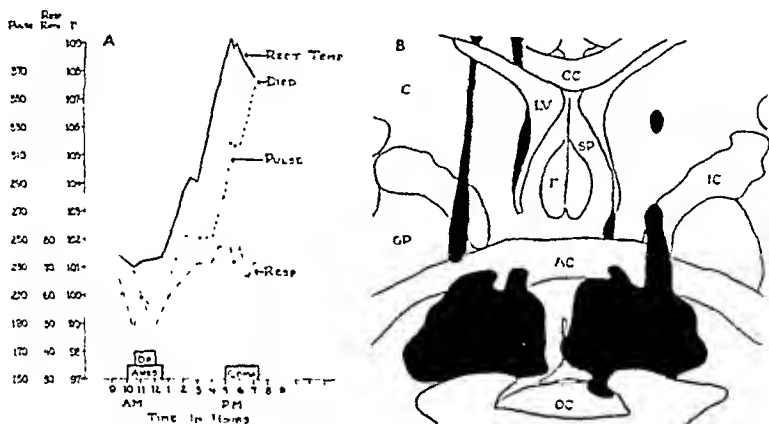


Fig. 4 (monkey 4).—*A*, temperature chart; *B*, lesions in the brain.

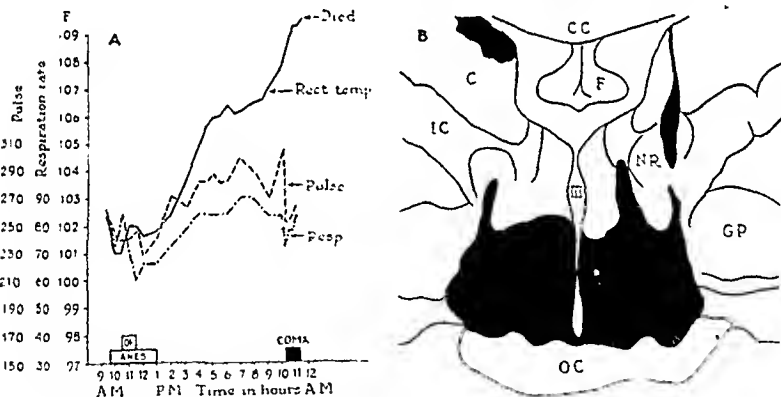


Fig. 5 (monkey 5).—*A*, temperature chart; *B*, lesions in the brain.

In monkey 5 the large bilateral lesion of the preoptic region and the anterior part of the hypothalamus seen in figure 5*B* was produced. The postoperative course is charted in figure 5*A*. The animal's temperature was maintained between 101 and 102 F. during the operation. One and one-half hours after operation, when the monkey appeared fully awake, its temperature began to rise and four hours later had reached 106 F. During the next three hours the temperature did not vary greatly, but thereafter rose rapidly and reached 109.1 F. eleven hours after operation. At this time the animal became comatose, but remained alive another forty-five minutes, the temperature at death being 109.5 F. The heart rate, between 230 and 250 per minute during and shortly after operation, showed some tendency to increase with the rise in temperature, the highest rate being 300 per minute. A slight increase in respiratory rate occurred. The

animal exhibited some piloerection and a little shivering during the latter part of the period of hyperthermia. Though the trunk felt very hot, the extremities remained cold, and the animal did not sweat.

The cases of these 2 monkeys illustrate severe, acute hyperthermia following appropriately situated injury to the temperature-regulating mechanism in the preoptic region and the anterior part of the hypothalamus. The rise in body temperature commenced one-half to one and one-half hours after operation, on recovery from the ether anesthesia, and proceeded to a peak above 109 F., when coma supervened and the animals died, seven and twelve hours after operation.

Reduction of Severe Hyperthermia with Soluble Pentobarbital.—In each of 7 other monkeys of the group with severe, acute hyperthermia, soluble pentobarbital proved an effective agent in reducing the hyperthermia, and with its aid 6 of the animals were brought through their

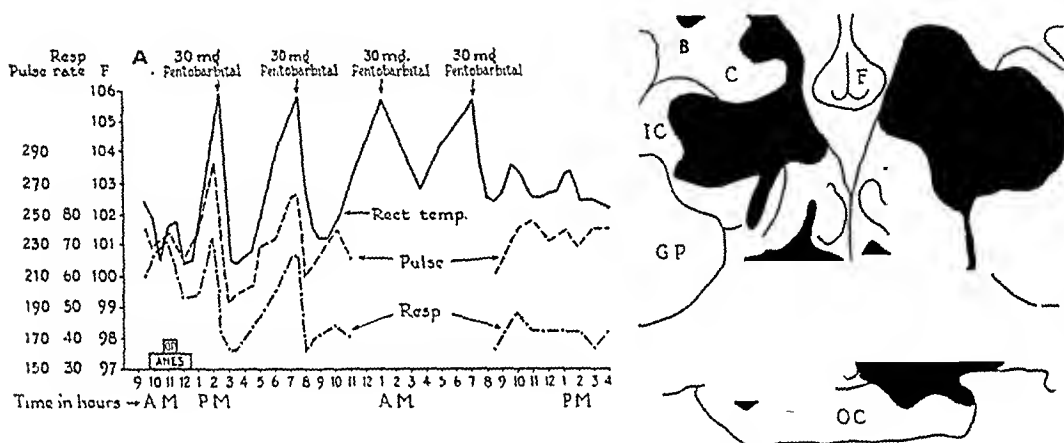


Fig. 6 (monkey 6).—A, temperature chart; B, lesions in the brain.

turbulent postoperative periods to survival. In administering pentobarbital in these cases, it was first essential to allow the hyperthermia to proceed to a point at which it became clear that the rise in temperature was severe, and if left unattended would probably proceed to death. Second, it was necessary to administer the drug before the hyperthermia had developed to the point at which the animal could no longer recover. In the single case of fatality in this group, pentobarbital was not given until the body temperature had reached 107 F.; in the remaining cases it was administered when the body temperature had reached 106 F. and as often thereafter as seemed desirable. The cases of each of the animals may be presented.

Monkey 6 suffered a large lesion of the preoptic region and the anterior portion of the hypothalamus, and anemic softening extended the destruction into the adjacent basal ganglia and the internal capsule on each side (fig. 6 B). Two and one-half hours after operation (fig. 6 A) its temperature had risen to 106 F., and 30 mg. of soluble pentobarbital was given intravenously. The temperature fell to 100.4 F., but eight hours after operation it had returned to 105.7 F. Thirty milligrams of soluble pentobarbital was again given, and the temperature fell to

101.2 F. Thirteen hours after operation the temperature had risen once more to 105.7 F., and again 30 mg. of soluble pentobarbital was given, the temperature falling to 102.8 F. A fourth peak of 105.6 F. was reached nineteen hours after operation, and a fourth injection of 30 mg. of soluble pentobarbital reduced the temperature to 102.4 F. The hyperthermia then appeared to have been definitely broken, though temperatures between 103 and 104 F. were subsequently encountered as late as the afternoon of the second postoperative day. On the third and fourth postoperative days the animal's temperature varied within the normal range, between 100.4 and 102.2 F. Because of its poor condition, which was attributed to the extensive lesion, the animal was killed on the fourth postoperative day.

In monkey 7 a small bilateral lesion of the preoptic region and the anterior portion of the hypothalamus was produced (fig. 7 *B*). As seen in figure 7 *A*, two hours after operation its temperature had risen to 106 F., and 40 mg. of soluble pentobarbital was given intravenously. The temperature fell to 103 F., but nine hours after operation it had again risen to 106.6 F. Forty milligrams of soluble

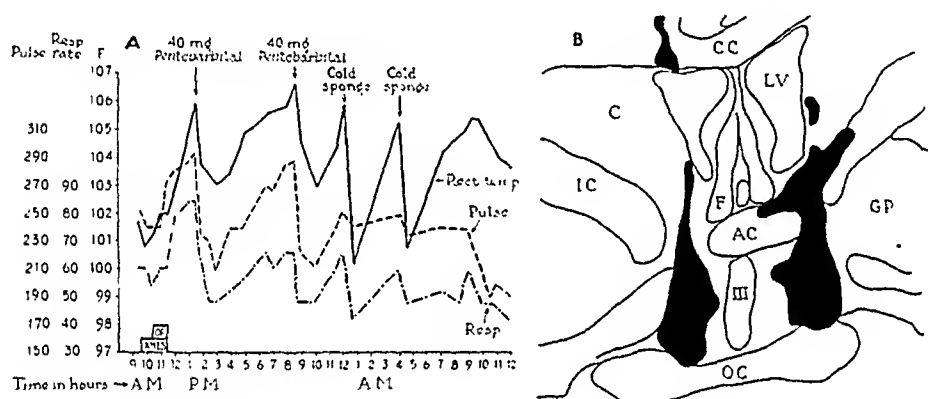


Fig. 7 (monkey 7).—*A*, temperature chart; *B*, lesions in the brain.

pentobarbital was again administered, and the temperature once more fell to 103 F. Twelve and sixteen hours after operation the animal's temperature had reached the third and fourth peaks, respectively, between 105 and 106 F., but on these occasions, with the back of the hyperthermia broken by pentobarbital, cold sponging proved effective in reducing the temperature. A fifth elevation, to 105.5 F., was encountered twenty-one hours after operation, but the temperature gradually fell without treatment, and on the second postoperative day the reading of 102.6 F. was almost within the normal range. The animal survived without further incident, and the results of subsequent tests of its temperature regulation in the chronic state will be presented in a later section.

In monkey 8 a small bilateral lesion of the preoptic region was produced (fig. 8 *B*). Two hours after operation (fig. 8 *A*) its temperature had risen to 106 F., and 40 mg. of soluble pentobarbital was given intravenously. The temperature fell to 102 F., but six hours after operation it had again risen to 106 F. Then 52 mg. of soluble pentobarbital was administered intraperitoneally, and a decided drop in temperature, to 98.2 F., resulted. Thirteen hours after operation the temperature had again risen to 105 F., but from this level it fell without further treatment to between 103 and 104 F. On the second postoperative day the hyperthermia was still present, and the animal was found in the morning with a temperature of 105.8 F. This was reduced by cold packing to

102.2 F., and the subsequent course of the animal was uneventful. Tests of its temperature regulation in the chronic state will be given later.

In monkey 9 a small preoptic lesion (fig. 9 *B*) resulted three hours after operation in a temperature of 106.1 (fig. 9 *A*). Forty milligrams of pentobarbital was given intravenously, and the temperature fell to 101.4 F. It subsequently rose to 105.8 F., but waned gradually and varied between 104 and 105 F., without further treatment, for about twenty-four hours after operation. The further course of the animal was uneventful, and the results of tests of temperature regulation in the chronic state will be given later.

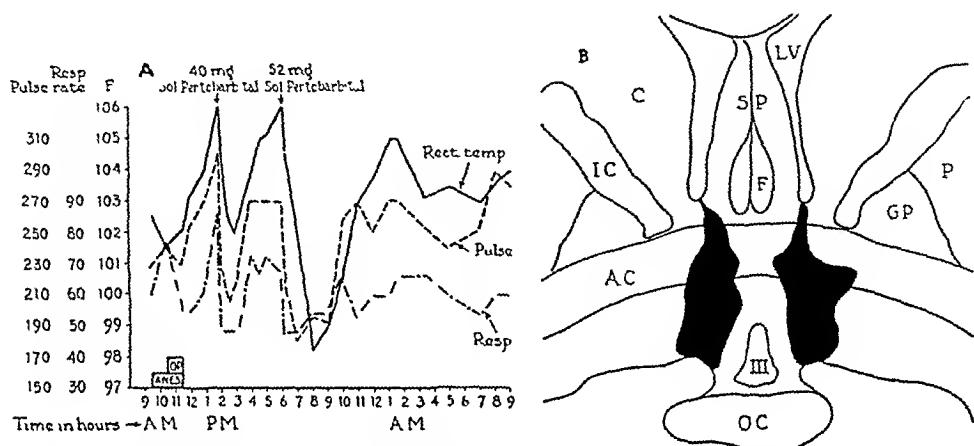


Fig. 8 (monkey 8).—*A*, temperature chart; *B*, lesions in the brain.

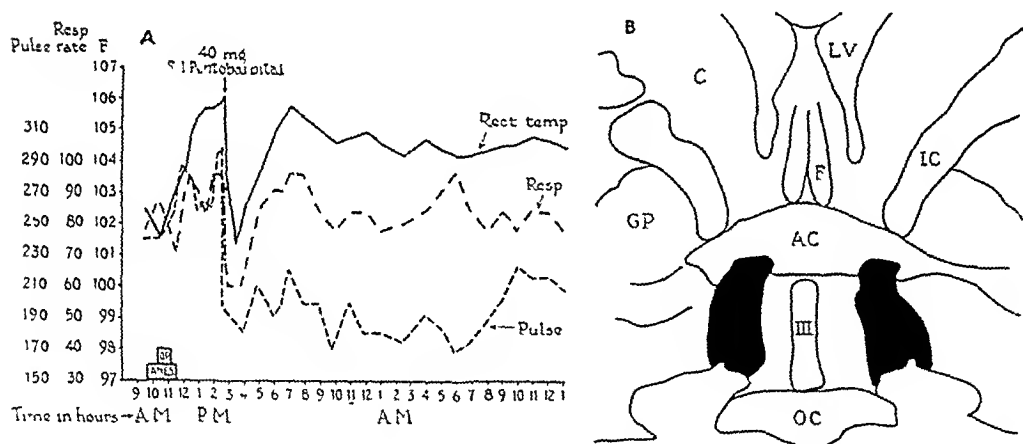
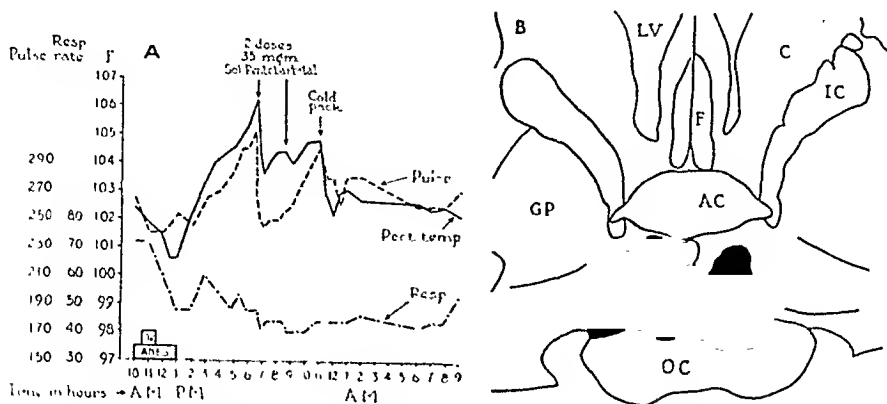


Fig. 9 (monkey 9).—*A*, temperature chart; *B*, lesions in the brain.

Monkey 10 suffered a lesion of the preoptic region and the anterior portion of the hypothalamus (fig. 10 *B*). The hyperthermia was more gradual than usual (fig. 10 *A*) but reached 106.1 F. seven hours after operation. Then 35 mg. of soluble pentobarbital was given intravenously, and the temperature fell to 103.6 F. Subsequent administration of 35 mg. of soluble pentobarbital subcutaneously had little further effect, but with cold packing eleven hours after operation the temperature was reduced to 102 F. and did not again rise greatly. The chronic course of the animal will be discussed later.

In monkey 11 a large lesion of the anterior part of the hypothalamus was produced (fig. 11 *B*). Five hours after operation (fig. 11 *A*) the temperature had risen to 106 F., and 35 mg. of soluble pentobarbital given half intravenously and half subcutaneously, resulted in a fall to 103 F. On a subsequent rise to 104 F.,

35 mg. of soluble pentobarbital was twice administered subcutaneously, with no immediate effects, but with a gradual fall to 102° F. The animal's further course will be considered later.



rose to reach 107 F. nineteen hours after operation. Then 40 mg. of soluble pentobarbital was administered intraperitoneally, and though the temperature fell to 102.2 F., the animal died three and one-half hours later. Autopsy showed no gross pathologic change, and death was attributed to the hyperthermia, which apparently was allowed to proceed for too long a time and to too high a level before treatment.

These animals taken as a group provide a clearcut demonstration of the efficacy of soluble pentobarbital as a therapeutic agent in reducing and controlling acute neurogenic hyperthermia. It is thought that the single fatality, that of monkey 12, to which pentobarbital was not administered until nineteen hours after operation, when the animal's temperature was 107 F., could have been avoided if the drug had been given earlier.

In monkeys 6 to 12 of this group, as well as in animals 4 and 5, piloerection and shivering were frequently noted during the course of the hyperthermia; the extremities remained cold, and no sweating occurred. The picture was one of paralysis of heat loss activity, with maintenance of action of heat conservation mechanisms. On administration of pentobarbital during the course of the hyperthermia, it was repeatedly observed that piloerection was relaxed, shivering ceased and the extremities became warm after injection. It seems clear, therefore, that at least a part of the effect of pentobarbital in reducing hyperthermia is to be attributed to its suppression of heat conservation activity. It may be pointed out, also, that in each experiment the hyperthermia was associated with an increase in the pulse and usually in the respiratory rate, alterations indicative of an increase in the metabolic processes of the body. It is not certain whether this increase was the cause or the result of the rise in body temperature, but it can be seen from the charts that in each case, after the injection of pentobarbital, the pulse and respiratory rates fell notably, and before body temperature had shown a great decline. It seems likely that, in addition to its suppression of heat conservation, pentobarbital also suppresses heat production.

The doses of soluble pentobarbital effective in reducing experimental hyperthermia were not large, 30 and 40 mg. in monkeys weighing 3 to 3.75 Kg. giving good results. These doses amount to approximately 10 to 12 mg. per kilogram, and are roughly one third of the usual dose of soluble pentobarbital required for surgical anesthesia in the monkey. The result in a single instance of injection of 52 mg. of soluble pentobarbital, or 17 mg. per kilogram, suggests that this quantity was somewhat excessive, for body temperature was reduced below normal. Three instances of subcutaneous injection, without effect or with only a very gradual fall in temperature, suggest that the constriction of peripheral vessels, which is one of the features of the hyperthermia, prevented or delayed the absorption of pentobarbital given subcutaneously and that intravenous or intraperitoneal injection is indicated.

Mild or Brief Hyperthermia.—In 7 experiments acute postoperative rises in temperature were encountered which either did not proceed as high or did not continue as long as in the experiments already presented. A group of 5 of these experiments may be distinguished in which lesions were placed in the preoptic region and the anterior portion of the hypothalamus, but in which the damage to the two halves of the brain was notably asymmetric. The animal which presented the highest rise in temperature of any of this group may be taken as an example.

In monkey 13 the lesion (fig. 13 *B*) was situated in the preoptic region and the anterior portion of the hypothalamus but was asymmetric, so that the entire medial part of the left side and much of the lateral portion of the right side of this region were spared. The temperature rose abruptly (fig. 13 *A*), to reach 105.8 F. three and one-half hours after operation, and then declined, to reach normal limits seven hours after operation. In the other animals with asymmetric

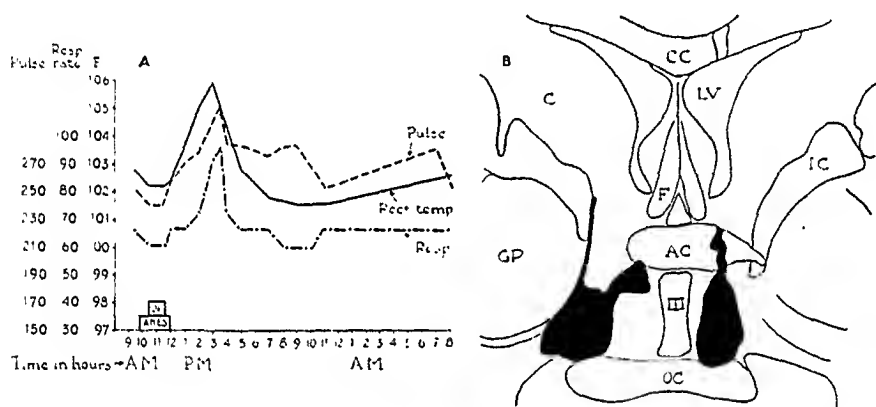


Fig. 13 (monkey 13).—*A*, temperature chart; *B*, lesions in the brain.

lesions the rises in temperature were not as high, the peaks being 105.4, 105, 104.9 and 103 F. respectively.

It seems reasonable to ascribe the mild nature of the hyperthermia in this group of animals to incomplete destruction of the bilaterally distributed mechanism for heat loss as a result of the asymmetric position of the lesions. In the 2 remaining animals the absence of marked and prolonged hyperthermia could be attributed to associated impairment of heat conservation facilities as a result of coincident injury to more caudal regions of the hypothalamus.

In monkey 14 the lesion was located more caudally than in the animals already considered, in the tuberal region of the hypothalamus (fig. 14 *B*). The animal's temperature (fig. 14 *A*) was not maintained well during the course of the operation and at its conclusion was only 97 F. The temperature climbed rapidly to within normal limits and then increased gradually, to reach a peak of 103 F. eight hours after operation. It then declined to within normal limits. In a second similar case there was a rise to 104 F. Tests of temperature regulation in the chronic state will be given later.

Postoperative Hypothermia.—In 2 animals of the present series a progressive fall in body temperature was encountered after operation. The lesions in these animals with hypothermia were subsequently observed to be located more caudally than was intended, in the tuberal and the anterior mamillary region of the hypothalamus. Monkey 15 is an example.

In monkey 15 the lesion was situated in the tuberal part of the hypothalamus (fig. 15 *B*) and extended backward to terminate above the mamillary bodies.

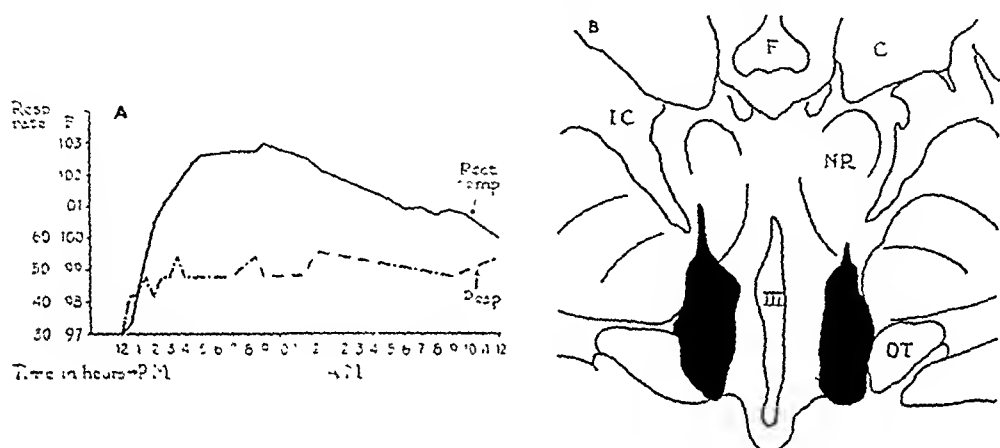


Fig. 14 (monkey 14).—*A*, temperature chart; *B*, lesions in the brain.

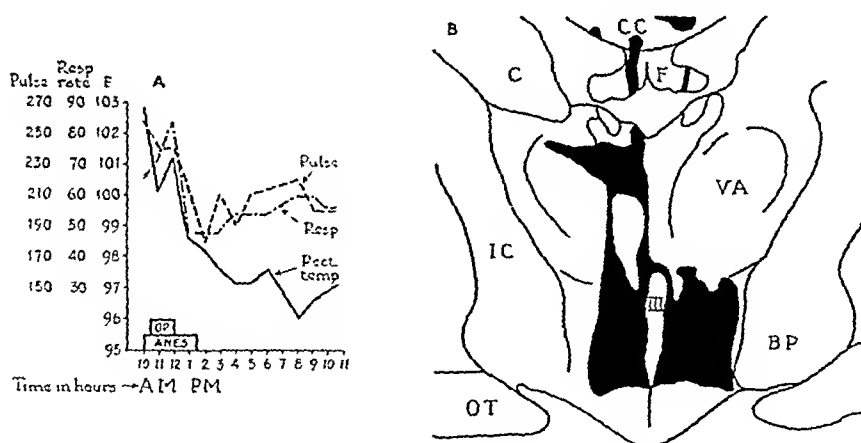


Fig. 15 (monkey 15).—*A*, temperature chart; *B*, lesions in the brain.

The animal's temperature (fig. 15 *A*) was 101.2 F. at the conclusion of the operation. When the animal was placed in a room at 80 F., its body temperature fell to 98.5 F. during the period of recovery from the ether anesthesia. Then, instead of rising to a normal level, as in the control animals, or becoming further elevated, as in the animals with hyperthermia, this animal's temperature continued to fall gradually, and from eight to ten hours after operation it ranged between 96 and 97 F., even though artificial heat was applied. The deficient temperature regulation in the chronic state will be discussed later.

General Consideration of the Acute Postoperative Results.—Before proceeding further, it is of interest to assemble the observations during

the acute postoperative period and to consider them from the point of view of the distribution of the lesions in the preoptic region and the hypothalamus. In each case the area of the lesion was projected on a reconstruction of the midsagittal plane; the projections from 2 control animals (monkeys 1 and 2), from all of the animals with severe hyperthermia (monkeys 4 to 12) and from an animal with postoperative hypothermia (monkey 15) are shown together in figure 16 *A*.

The lesions in hyperthermic monkeys 4 to 12 (shaded in figure 16 *A*) are seen to be clustered in the preoptic region and the anterior portion of the hypothalamus and to be distributed chiefly between the anterior commissure and the optic chiasm. Since destruction of this region was followed by a severe postoperative rise in temperature, in the course of which heat loss activity remained paralyzed, it is reasonable to conclude

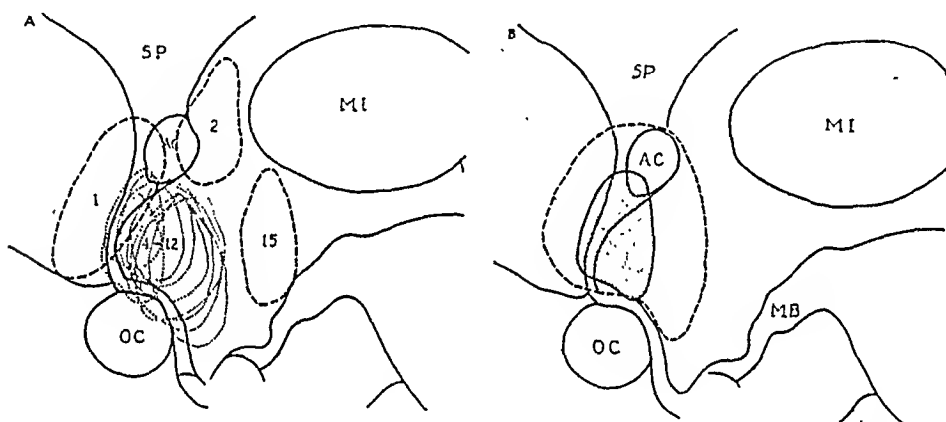


Fig. 16.—*A*, outlines of lesions in the brains of monkeys 1, 2, 4 to 12 and 15 projected on a drawing of a medial sagittal section of the brain.

B, projection on a medial sagittal section of a monkey's brain of the center which responds to local heating by activating the heat loss mechanisms. The stippled area represents the main part of the center, which is surrounded by a less active region enclosed by the broken line.

that within this region are situated neural mechanisms essential for the initiation and regulation of processes for body cooling.

Further evidence for this view, derived from a different experimental approach, is presented in figure 16 *B*, which depicts as projected on the midsagittal plane the region of the monkey's brain the local heating of which results in activation of heat loss mechanisms. It has been shown by Beaton, McKinley, Berry and Ranson¹¹ that in the anesthetized monkey warming this region with high frequency current passed between

11. Beaton, L. E.; McKinley, W. A.; Berry, C. M., and Ranson, S. W.: Localization of Cerebral Center Activating Heat-Loss Mechanisms in Monkeys, *J. Neurophysiol.* 4:478-485, 1941.

the tips of otherwise insulated electrodes results in excess sweating, vasodilatation and accelerated respiration, which give every appearance of being identical with the integrated response of the normal animal to an elevated environmental temperature. The reconstructed aspect of this heat-sensitive area (fig. 16 *B*), not hitherto presented, is included here for comparison with the distribution of lesions which, in monkeys 4 to 12 of the present investigation (fig. 16 *A*), were followed by severe postoperative hyperthermia. The distribution of the two regions coincides closely, and the two lines of evidence complement one another in a fashion which points to a single conclusion, namely, that the preoptic region and the anterior region of the hypothalamus are the site of a center for heat loss.

It seems clear that the hyperthermia which followed injury to the preoptic region and the anterior end of the hypothalamus in these experiments is to be attributed to the destruction of a specific neural mechanism for heat loss located within this area, and not to the interruption of long pathways which might simply be passing through this part of the brain from other levels. Lesions in monkeys 1 and 2, located anterior and dorsal to the preoptic region and the anterior part of the hypothalamus (fig. 16), were not followed by hyperthermia, nor did hyperthermia follow the laterally placed lesions in monkey 3 (fig. 3). The caudal lesion in monkey 15 (fig. 16 *A*) was followed by postoperative hypothermia, due, undoubtedly, to injury of the heat conservation mechanism, which Ranson, Fisher and Ingram¹² and Ranson¹³ have shown to be most effectively thrown out of function by lesions of the posterior portion of the hypothalamus.

Descending pathways from the anterior portion of the hypothalamus were also interrupted by the lesions in monkey 15, and the animal exhibited chronic impairment in the ability to defend itself against overheating. This result suggests that there is more to the etiology of hyperthermia than simply the destruction of the heat loss mechanism. Pertinent observations derived from tests for temperature regulation in the chronic state made on all surviving monkeys may be presented before the problem is considered further.

TEMPERATURE REGULATION IN THE CHRONIC STATE

Control Animals.—As has already been mentioned, monkeys 1, 2 and 3, with lesions anterior, dorsal and lateral, respectively, to the preoptic region and the anterior portion of the hypothalamus, showed

12. Ranson, S. W.; Fisher, C., and Ingram, W. R.: Hypothalamic Regulation of Body Temperature in the Monkey, *Arch. Neurol. & Psychiat.* **38**:445-466 (Sept.) 1937.

13. Ranson, S. W.: Regulation of Body Temperature, *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:342-399, 1940.

no impairment in temperature regulation in the chronic state. When tested from four to five weeks after operation, they exhibited good piloerection and violent shivering on exposure to cold and profuse sweating on exposure to heat, at thresholds of body temperature which were similar to those encountered in preoperative tests.

Animals with Severe Hyperthermia.—Five of the monkeys with severe hyperthermia in the acute postoperative period were tested in the chronic state. Two of these animals showed chronic impairment in the ability to defend themselves against overheating, with maintained, though not perfectly normal, ability to guard against excessive cooling.

Monkey 11, with the large lesion in the anterior portion of the hypothalamus, shown in figure 11, was kept for five weeks after operation. During this time the animal showed a tendency to a slightly subnormal or considerably elevated temperature, according to whether the environmental temperature was low or high. The temperature regulation was tested on two occasions, three and five weeks after operation. At both trials the animal showed marked piloerection and vigorous shivering on exposure to cold, but on neither occasion did it sweat or exhibit vasodilatation on exposure to heat, even though the rectal temperature was elevated in the trials to 105.5 and 105.7 F. Similar results were encountered in monkey 10.

The 3 remaining animals with initial severe hyperthermia, monkeys 7, 8 and 9, showed normal regulation to both heat and cold in the chronic state. The lesions in these animals (figs. 7 to 9) were small, sparing some of the lateral and a considerable amount of the medial part of the preoptic region. When the lesion was viewed in reconstruction, it was evident, also, that the injury did not extend as far caudally into the anterior portion of the hypothalamus as did the larger lesions in monkeys 10 and 11. It is suggested that the heat loss mechanism was initially thrown completely out of function by the partial destruction of the preoptic region and the anterior portion of the hypothalamus in monkeys 7, 8 and 9, but that the margin of safety in this mechanism was sufficiently great for the remaining parts to maintain normal heat loss function in the chronic state. The enduring paralysis of heat loss activity with the more extensive destruction of the preoptic region and the anterior portion of the hypothalamus in monkeys 10 and 11 argues against a compensatory function being assumed by some other part of the brain.

Animals with Mild Hyperthermia.—Normal or only slightly subnormal heat regulation in the chronic state in the 5 monkeys with asymmetric lesions of the preoptic region and the anterior portion of the hypothalamus, of which monkey 13 (fig. 13) is an example, also suggests that while partial injury to the heat loss mechanism is sufficient to impair its function more or less completely in the acute period, in the chronic state the uninjured parts will maintain normal, or almost normal, activity.

Monkey 14, as well as a second similar animal, which exhibited mild hyperthermia after symmetrically placed lesions in the tuberal portion of the hypothalamus (fig. 14), maintained normal body temperatures under laboratory

conditions during its survival of five weeks. Tests of regulation against heat made two and five weeks after operation showed complete loss of sweating, though the body temperature was elevated to 106.1 F. in both trials. A test of regulation against cold five weeks after operation showed an impaired reaction, with only slight piloerection and shivering. The paralysis of heat loss function, which remained as extreme as in the animals with destruction of the preoptic region and the anterior portion of the hypothalamus, indicates that the mechanism for heat loss either extends into the tuberal part of the hypothalamus or sends its efferent pathway backward through the lateral part of this region. This animal's failure to exhibit more pronounced hyperthermia in the acute postoperative period may be attributed to the coincident injury of the heat conservation mechanism, indicated by its impaired regulation against cold in the chronic state.

Animals with Postoperative Hypothermia.—Monkey 15, and a second similar animal, which exhibited acute postoperative hypothermia after lesions of the tuberal and anterior mamillary parts of the hypothalamus (fig. 15), did not regain the ability to keep the body temperature up to the normal level under ordinary laboratory conditions. During a survival of three weeks monkey 15, which was kept much of the time in an incubator at 86 F., frequently exhibited temperatures as low as 95 F. No shivering or piloerection was ever observed, even in response to extreme cold. On exposure to heat three weeks after operation, reddening of the chest was noted, but no sweating occurred, though the body temperature was elevated to 105.5 F. In the second animal neither sweating nor vasodilatation occurred, though the animal's temperature was elevated to 106.8 F.

The paralysis of heat loss activity in these 2 animals may be attributed to interruption of the efferent pathway for heat loss descending from more anterior levels of the hypothalamus. It seems unlikely that the heat loss mechanism itself extends into the caudal part of the hypothalamus, for heat loss activity may be abolished by more anterior lesions, which leave the caudal portion of the hypothalamus intact (see report on monkey 11). With the heat loss mechanism paralyzed, the failure of monkey 15 and its mate to exhibit postoperative hyperthermia may be ascribed to coincident paralysis of the heat conservation mechanism, the activity of which appears essential for the acute postoperative elevation in temperature. When the latter mechanism was infringed on by tuberal lesions (monkey 14), only mild hyperthermia resulted. When it was destroyed (monkey 15), not only did the temperature fail to rise after operation, but hypothermia resulted. In another paper evidence was presented to show that hypothermia regularly results from bilateral lesions in the posterior part of the hypothalamus (Ranson¹³).

The fall of body temperature after a lesion in the posterior portion of the hypothalamus and that after the injection of pentobarbital appear to have a common basis, a block of the heat conservation mechanism.

This raises the question whether the antipyretic action of pentobarbital may not be effected at the hypothalamic level. Without any rash commitments, it can be pointed out that Fulton,¹⁴ Masserman¹⁵ and Hodes and Magoun¹⁶ have reported a decrease of hypothalamic excitability during anesthesia induced with pentobarbital.

COMMENT

At least two factors appear to be operative in the production of postoperative hyperthermia. First, the heat loss mechanism must be thrown out of function. Second, and just as important, the heat conservation mechanism must retain its activity. In these experiments, observations on the monkeys revealed increased activity of the heat conservation mechanism during hyperthermia, but this increase was not always maximal or continuous. Coldness of the extremities was an enduring feature; piloerection and shivering occurred only intermittently and were never extreme in degree. The question, therefore, may be raised whether a third factor, that of increased heat production, is also operative during the period of hyperthermia. Calorimetric tests would be necessary for a definite answer to this question, but observation of increased pulse and respiratory rates, indicative of increased metabolic activity, is suggestive. If increased heat production is an essential part of severe hyperthermia, it, too, would appear to be dependent on the integrity of the caudal part of the hypothalamus.

Little attention has heretofore been directed to the reasons for the disappearance of the acute postoperative hyperthermia. The increased activity of the heat conservation, and possibly also of the heat production mechanism, which appears to be the active feature of this disorder, is for some reason only short lasting. In the surviving animals in the present study, the elevation of body temperature never persisted beyond the second postoperative day. Its abatement is not necessarily to be ascribed to recovery of heat loss activity, for in acutely hyperthermic monkeys 10 and 11 the paralysis of this activity endured for several weeks. It is possible that surrounding the lesions which destroy the heat loss mechanism in the preoptic region and the anterior portion of the hypothalamus is a zone extending into the posterior part of the hypothalamus in which edema, or a concentration of breakdown products, or some other unknown agent, exerts a short-lasting (one or

14. Fulton, J. F.: *Physiology of the Nervous System*, New York, Oxford University Press, 1938.

15. Masserman, J. H.: Effects of Analeptic Drugs on the Hypothalamus of the Cat, *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:624-634, 1940.

16. Hodes, R., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Forebrain and Midbrain with Special Reference to the Pupil, *J. Comp. Neurol.* **76**:169-190, 1942.

two day) irritation. It is also possible that reciprocal inhibitory connections exist between the hypothalamic mechanism for heat loss and that for heat conservation, so that destruction of the first is associated with exaggerated activity of the second, as a short-lasting release phenomenon.

The present study has provided ample demonstration in monkeys of a sharp postoperative rise in body temperature following injury to the anterior region of the hypothalamus. During the rise in temperature there are absence of sweating, a warm trunk but cold extremities, pronounced tachycardia and some hyperpnea and intermittent piloerection and shivering. If the animal is left untreated, the temperature may rise to a fatal level. The disorder constitutes acute neurogenic hyperthermia, and we see no reason to distinguish it from the hyperthermia which frequently follows acute injury to the hypothalamic region in man.

The evidence points to a twofold cause of experimental hyperthermia. The disorder involves, first, paralysis of the central mechanism for heat loss and, second, the maintained or increased activity of the central mechanism for heat conservation, and perhaps also for heat production. The combination of these conditions results in an elevation of body temperature which the animal is powerless to dissipate. The normal balance of the temperature-regulating mechanisms is lost, and the scale is weighted toward the side of heat conservation and heat production. Attempts to control the disorder by the administration of central-acting antipyretics which normally excite the heat loss mechanism might be expected to fail, because paralysis of the central mechanism for heat loss is one of the precipitating features of the condition.

Compelling evidence has been presented in this study for the value of soluble pentobarbital in reducing and controlling experimental hyperthermia. The administration of pentobarbital appears to correct the imbalance in the temperature-regulating mechanisms by suppressing the activity of the mechanism for heat conservation and heat production. After injection of soluble pentobarbital during hyperthermia in these experiments, piloerection was relaxed and shivering ceased; the cold extremities became warm, and the pulse and respiratory rates were decreased. The body temperature fell to a normal level, or, with greater concentrations of pentobarbital, to a subnormal level. A single injection of soluble pentobarbital was effective in reducing body temperature for a period of only three to six hours, but because the effective doses were of hypnotic, rather than of anesthetic, concentration, repeated doses could be administered.

We should like to suggest that the striking efficacy of soluble pentobarbital in reducing experimental hyperthermia in the monkey warrants

its trial in the treatment of neurogenic hyperthermia following acute injury to the brain in man, the incidence of which in these times may be expected to be increased.

SUMMARY

Bilateral injury to the rostral region of the hypothalamus in a series of monkeys results in an acute postoperative rise in body temperature, which if untreated proceeds to a fatal level.

This experimental hyperthermia is the result of central paralysis of the heat loss mechanism, associated with maintained or exaggerated activity of the central mechanism for heat production and heat conservation.

Intravenous administration of soluble pentobarbital (pentobarbital sodium) during the course of the hyperthermia suppresses the activity of the mechanism for heat conservation and heat production and reduces body temperature to the normal level. When administered subcutaneously, pentobarbital is relatively ineffective.

The striking efficacy of pentobarbital in reducing experimental hyperthermia in the monkey warrants its trial in the treatment of neurogenic hyperthermia following acute injury to the brain in man.

303 East Chicago Avenue.

MYASTHENIA GRAVIS

CURARE SENSITIVITY; A NEW DIAGNOSTIC TEST AND APPROACH TO CAUSATION

A. E. BENNETT, M.D.

OMAHA

AND

CAPTAIN PAUL T. CASH

MEDICAL CORPS, ARMY OF THE UNITED STATES

In previous investigations¹ with standardized curare² one of us (A. E. B.) has called attention to the similarity of the action of curare and the symptoms of myasthenia gravis. After these clinical observations we discovered the same hypothesis had been suggested by others: Oppenheim³ in 1901 observed that "veratrine evoked in muscles a condition analogous to myasthenia"; Briscoe⁴ in 1936 showed that mild curarization produced a myogram similar to that of myasthenia gravis, and later Harvey and his co-workers⁵ confirmed this similarity and stated, "The characteristic abnormalities of the electrical responses of the myasthenic and curarized muscle are identical in all respects." From the analogy between myasthenia gravis and partial curarization he sug-

From the Department of Neuropsychiatric Research, Bishop Clarkson Memorial Hospital, and the Department of Neurology of the University of Nebraska College of Medicine.

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1. Bennett, A. E.: Curare: A Preventive of Traumatic Complications in Convulsive Shock Therapy, *Am. J. Psychiat.* **97**:1040 (March) 1941; Clinical Investigations with Curare in Organic Neurologic Disorders, *Am. J. M. Sc.* **202**: 102 (July) 1941.

2. E. R. Squibb & Sons furnished the standardized curare used in these experiments. We have also been using crystalline curare, described by O. Wintersteiner and J. D. Dutcher (*Science* **95**:10 [May 1] 1942).

3. Oppenheim, H.: *Die myasthenische Paralyse*, Berlin, S. Karger, 1901, p. 107.

4. Briscoe, G.: The Antagonism Between Curarine and Prostigmin and Its Relation to the Myasthenia Problem, *Lancet* **1**:469 (Feb. 29) 1936.

5. Harvey, A. M., and Masland, R. L.: The Electromyogram in Myasthenia Gravis, *Bull. Johns Hopkins Hosp.* **69**:1 (July) 1941. Harvey, A. M., and Lilienthal, J. L.: Observations on the Nature of Myasthenia Gravis, *ibid.* **69**:566 (Dec.) 1941.

gested the hypothesis that a circulating inhibitor substance may arise from the thymus gland. Harvey and his associates ⁶ concluded:

All of the experimental work, therefore, points to the similarity of myasthenia to a mild curarization; it thus seems likely that the defect in the disease, as in curarization, is due to an elevation of the threshold of the motor end-plates to the effects of the nerve impulses reaching them.

In myasthenia gravis there is some interference in transmission of nerve impulses across the myoneural junction; there may also be some disorder of muscle metabolism. Since acetylcholine (Dale, Feldberg and Vogt ⁷) is the chemical mediator of neuromuscular transmission, some abnormality in the action of acetylcholine seems likely in myasthenia gravis. Physostigmine (Walker ⁸), which restores normal neuromuscular performance in most myasthenic patients, is known to hinder destruction of acetylcholine by choline esterase. There seems to be no direct evidence that acetylcholine is lacking or destroyed in cases of myasthenia. We have found that intravenous administration of acetylcholine does not improve myasthenic symptoms; this suggests there is no deficiency of acetylcholine in myasthenia gravis. However, Lanari,⁹ giving acetylcholine intra-arterially, obtained contraction of myasthenic muscle. There is no increase in choline esterase either in the serum or in muscle to account for an increased destruction of acetylcholine. Therefore the evidence of any deficiency of acetylcholine in the disease is inconclusive.¹⁰

Keisser and Neuschlab¹¹ demonstrated that curare inhibits the action of acetylcholine. The principle of the antagonistic action of curare and acetylcholine on a frog gastrocnemius muscle preparation can be used as a method of assay of the potency of curare. According to Holaday, addition of acetylcholine to a frog gastrocnemius muscle preparation produces a contraction which if recorded isometrically furnishes a reference height for comparison with a decreased height of contraction obtained through the inhibitory effect of a solution of curare. Curare thus seems to raise the threshold of muscle contraction to acetylcholine; according to

6. Gammon, G. D.; Harvey, A. M., and Masland, R. L.: On the Nature of Certain Diseases of the Voluntary Muscles, Biological Symposia, Lancaster, Pa., Jacques Cattell Press, 1941, vol. 3, pp. 292-297.

7. Dale, H. H.; Feldberg, W., and Vogt, M.: Release of Acetylcholine at Voluntary Motor Nerve Endings, *J. Physiol.* **86**:353 (May 4) 1936.

8. Walker, M. B.: Case Showing Effect of Prostigmin on Myasthenia Gravis, *Proc. Roy. Soc. Med.* **28**:759 (April) 1935.

9. Lanari, A.: A Pharmacologic Study of the Myotonic Muscle, *Arch. internat. de pharmacodyn. et de thérap.* **61**:360 (March 31) 1939.

10. McGeorge, M.: Choline Esterase Activity in Disease, with Special Reference to Myasthenia Gravis, *Lancet* **1**:69 (Jan. 9) 1937.

11. Keisser, O., and Neuschlab, S. M.: Antagonism of Acetylcholine and Curare, *Arch. f. exper. Path. u. Pharmacol.* **91**:356, 1921.

Harvey, it inhibits muscular action by altering the threshold of muscle response to acetylcholine. These observations have also been reported in experiments by Hodes and Steiman.¹² Harris and Harris¹³ found that very small amounts of curare have a pronounced inhibitory effect on choline esterase activity of human serum; this observation has been confirmed by other investigators.^{13a} Chronaxia is increased both in myasthenic and in curarized muscle according to Djuricic and Vujic.¹⁴ After injection of prostigmine methylsulfate it is decreased.

There is some evidence in favor of an additional primary disturbance of muscle metabolism. There is a decided increase in potassium in myasthenic muscles according to Cumings¹⁵; prostigmine produces a fall in the amount of muscle potassium, with a rise in the potassium of the serum and the red blood cells but with no increase in urinary excretion. The administration of potassium in large amounts benefits myasthenic patients. An increased potassium ion concentration tends to improve conduction at nerve terminals in voluntary muscle. Ephedrine and guanidine hydrochloride¹⁶ seem to increase the sensitivity of striate muscle to acetylcholine and to relieve the asthenia and parietic symptoms of the disease but do not affect choline esterase activity. Stare and Ricketts¹⁷ found that myasthenic muscles consume less oxygen than do normal muscles. Injection of prostigmine methylsulfate increases the consumption of oxygen, which suggests some abnormality in intermediary metabolism.

Other evidence of primary muscle disorder in the disease is suggested by Milhorat's¹⁸ observations that with advanced stages of myasthenia

12. Hodes, R., and Steiman, S. E.: The Effects of Acetylcholine and Eserine on Frog Muscle, *Am. J. Physiol.* **127**:470-479 (Oct.) 1939.

13. Harris, M. M., and Harris, R. S.: Effect in Vitro of Curare and Beta-Erythroidin Hydrochloride on Choline Esterase of Human Blood Serum, *Proc. Soc. Exper. Biol. & Med.* **46**:619 (April) 1941.

13a. A. R. McIntyre and R. E. King (D Tubocurarine Chloride and Choline Esterase, *Science* **97**:69 [Jan. 15] 1943) found that all crude curare preparations examined inhibit serum choline esterase, while the chemically pure (D tubocurarine chloride) preparation is devoid of this action. The inhibitory activity of crude curare preparations on choline esterase is not necessarily related to their paralytic action.

14. Djuricic, I., and Vujic, V.: Contributions to the Problem of Therapy in Myasthenia Gravis Pseudoparalytica, *Arch. f. Psychiat.* **111**:48 (Jan. 10) 1940.

15. Cumings, J. N.: Potassium and Muscular Disorders, *J. Neurol. & Psychiat.* **4**:226 (July-Oct.) 1941.

16. Minot, A. S.; Dodd, K., and Riven, S. S.: Use of Guanidine Hydrochloride in Treatment of Myasthenia Gravis, *J. A. M. A.* **113**:553 (Aug. 12) 1939.

17. Stare, F. J., and Ricketts, H. T.: The in Vitro Respiration of Muscle in Myasthenia Gravis, personal communication to the author.

18. Milhorat, A. T.: Studies in Diseases of Muscle, *Arch. Neurol. & Psychiat.* **46**:800 (Nov.) 1941.

prostigmine has practically no effect or else increasing amounts are necessary to depress the choline esterase to lower levels. This phenomenon was limited to the response of voluntary muscles, which became increasingly refractory to stimulation. No diminishing effect of prostigmine on the activity of choline esterase was demonstrated. In the terminal stages of myasthenia patients showed serious involvement of creatine metabolism, which had been normal before. For these patients administration of prostigmine was ineffective; in other seriously ill patients who responded to prostigmine the creatine was normal.

None of these mechanisms is completely understood. According to Goodman and Gilman:¹⁹

The pathological physiology of myasthenia may be due to: (1) a deficiency in the amount of acetylcholine produced at motor nerve endings, (2) an increase in muscle choline esterase, and (3) the existence of some abnormal substance or metabolite with a curare-like action which elevates the threshold of skeletal muscle to the effects of nerve stimuli; which of these factors is involved is not known.

Because curarization produces all the manifestations of myasthenia and myasthenic patients are exceedingly sensitive to the drug, it appears likely that some foreign substance similar in chemical action to curare initiates myasthenia by inhibiting or neutralizing the action of acetylcholine.

Quinine, which has a weak curare-like action, also aggravates myasthenia and relieves the opposite condition, myotonia congenita. Milhorat expressed the opinion that the action of quinine suggested the nature of the disease and could be used in diagnosis; this confirms our contention, but the specific action of standardized curare is more accurate. Harvey²⁰ and we²¹ have likewise demonstrated that quinine methochloride produces a myasthenic reaction, the effects of which are relieved by prostigmine.

The pharmacologic action of curare is entirely on the neuromuscular junction; it inhibits, anatognizes or blocks acetylcholine and practically abolishes the transmission of nerve impulses. Physostigmine is a specific antidote for curare intoxication. The symptoms produced in the patient by varying doses of curare are exactly those of myasthenia gravis; they progress according to dosage, just as myasthenia progresses from mild to severe stages and end in paralysis of the respiratory muscles. In other words, curare poisoning produces artificial myasthenia gravis.

19. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941, p. 342.

20. Harvey, A. M.: The Action of Quinine Methochloride on Neuromuscular Transmission, *Bull. Johns Hopkins Hosp.* **66**:52 (Jan.) 1940.

21. Bennett, A. E., and Cash, P. T.: Curarization with Quinine Methochloride to Prevent Traumatic Complications of Metrazol Shock Therapy, *Psychiatric Quart.* **15**:351 (April) 1941.

These observations indicate that the myasthenic patient would exhibit an increased degree of sensitivity to curare. We have found this to be true. In 5 patients with myasthenia gravis, all showing decidedly different stages of the disease, we found that one twentieth to one fifth (5 to .15 mg.) of the average adult dose of standardized curare necessary to produce generalized paresis in a normal subject causes profound exaggeration of symptoms in myasthenic patients. The results of these studies have been recorded in motion pictures. From these observations we have concluded that curare can be safely used as a specific diagnostic test for myasthenia gravis, just as prostigmine methylsulfate²² is now used in the opposite direction, but is not always conclusive. In doubtful cases in which the response to the prostigmine test is indefinite we believe curare will produce a more specific reaction.

These observations suggest that the etiologic agent in myasthenia gravis is some form of curare intoxication. Possibly with overactivity of the thymus gland there is elaborated a substance which has a curare-like action, similar to that of thyroxin in exophthalmic goiter. The evidence for this assumption is the fairly constant pathologic observation at necropsy of enlargement or tumor of the thymus,²³ the relief of myasthenia by irradiation of the thymus and thymectomy²⁴ and Adler's²⁵ observations on experimental muscular weakness resembling myasthenia in young animals with thymus gland transplants. These symptoms were relieved by prostigmine. Adler also produced asthenia with extracts of the thymus gland. Indirect evidence is the common association of exophthalmic goiter and myasthenia.²⁶ Mild myasthenia occurs in cases of exophthalmic goiter, in which it is known that the thymus gland hypertrophies. Both myasthenia and hyperthyroidism have been relieved by thyroidectomy.²⁷ Some investigators, disagreeing with the thymus

22. Viets, H. R., and Schwab, R. S.: Prostigmin in the Diagnosis of Myasthenia Gravis, *New England J. Med.* **213**:1280 (Dec. 26) 1935.

23. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, *Arch. Path.* **29**: 212 (Feb.) 1940. Blalock, A.: Tumors of the Thymic Region and Myasthenia Gravis, *Am. J. Surg.* **54**:149 (Oct.) 1941.

24. Blalock, A.; Mason, M. F.; Morgan, H. J., and Riven, S. S.: Myasthenia Gravis and Tumor of the Thymic Region, *Ann. Surg.* **110**:544 (Oct.) 1939. Blalock, A.; Harvey, A.; Ford, F. F., and Lilienthal, J. L.: The Treatment of Myasthenia Gravis by Removal of the Thymus Gland, *J. A. M. A.* **117**:1529 (Nov. 1) 1941. Campbell, E.; Fradkin, N. F., and Lipetz, B.: Myasthenia Gravis Treated by Excision of Thymic Tumor, *Arch. Neurol. & Psychiat.* **47**:645 (April) 1942.

25. Adler, H.: Thymus und Myasthenie, *Arch. f. klin. Chir.* **189**:529, 1937.

26. Cohen, S. J., and King, F. H.: Relation Between Myasthenia Gravis and Exophthalmic Goiter, *Arch. Neurol. & Psychiat.* **28**:1338 (Dec.) 1932.

27. Kowallis, G. F.; Haines, S. F., and Pemberton, J. deJ.: Goiter with Associated Myasthenia Gravis, *Arch. Int. Med.* **69**:41 (Jan.) 1942.

theory, have expressed the belief that the adrenals²⁸ are more likely responsible. It seems reasonable to believe that future studies of the causal agent responsible for myasthenia should be directed along neurophysiologic and biochemical lines in order to determine why myasthenic patients have chronic curare-like poisoning.

The following histories illustrate our experiments with curare in cases of myasthenia and suggest the technic and dosage of standardized curare that may be used as a specific diagnostic test.

CASE 1.—Mrs. V. P., aged 31, in 1939 had progressive difficulty in speaking; six months later dysphagia developed, together with remittent ptosis and diplopia. All the symptoms became progressive; the voice was inarticulate at times; great difficulty in movements of the tongue developed, and attempts to swallow caused choking spells. The trunk and extremities were uninvolved; a loss in weight of 25 pounds (11.3 Kg.) occurred.

Examination revealed undernutrition, bilateral ptosis, loss of upward conjugate movements of the eyes, expressionless facies, inability to elevate or completely protrude the tongue and almost complete anarthria. Otherwise, a complete examination revealed nothing abnormal.

Prostigmine Diagnostic Test.—Injection of 1.5 mg. of prostigmine methylsulfate with 1/100 grain (0.6 mg.) of atropine sulfate resulted in a 4 plus score, presumptive evidence of myasthenia gravis.

Curare Diagnostic Test.—The patient's weight was 100 pounds (45.4 Kg.). The average curarizing dose for a person of this weight would be 50 mg. (1 mg. per two pounds [1.8 Kg.]) of standardized curare to produce mild partial generalized motor paresis. One-tenth this dose, or 5 mg. of curare principle, was slowly injected intravenously over a period of one minute. Immediately at the end of injection the patient showed complete bilateral ptosis, external ophthalmoplegia, complete loss of all movements of the tongue, flaccid paresis of the muscles of the neck, almost complete flaccid paresis of all extremities and respiratory difficulty. The height of the reaction came about two minutes after injection, when 1.5 mg. of prostigmine methylsulfate with 1/100 grain (0.6 mg.) of atropine sulfate was injected intravenously. Within two minutes after the injection all evidence of acute curare intoxication was gone, and most of the myasthenic symptoms were relieved.

CASE 2.—J. L., a man aged 54, for about ten years had had recurrent attacks of ptosis and inability to move the eyeballs; the attacks gradually progressed in frequency and severity. For about one year the patient had been conscious of almost constant inability to focus the eyes or rotate the eyeballs. Recently he noticed bulging of the left eye, huskiness of the voice after excessive talking and difficulty at times in swallowing.

Examination revealed that the left eye was exophthalmic, with the lid practically immobile; it measured 17 mm. with the Luedde exophthalmometer and the right 12 mm.; the right eyelid could be raised slightly with compensatory action of the frontalis muscle. Both eyes were fixed centrally; no motility whatever could be elicited. The facies was smooth, with a typical myasthenic expression; otherwise, complete examination revealed nothing abnormal.

28. Bomskov, C., and Milzney, G.: Involvement of the Thymus in Myasthenia Gravis Pseudoparalytica, *Arch. Neurol. & Psychiat.* **47**:488 (March) 1942; abstracted from *Deutsche Ztschr. f. Chir.* **254**:99 (Oct. 19) 1940.

Prostigmine Diagnostic Test.—The response was doubtful, and daily intramuscular injections of the drug and oral medication gave only slight temporary relief of the ocular symptoms. Additional therapy with guanidine and adrenal cortex extract with lecithin also gave no relief.

Curare Diagnostic Test.—Several intravenous injections of one-tenth to one-fifth the average dose of standardized curare were given. Since the patient weighed 160 pounds (72.6 Kg.), the average dose necessary to produce generalized curarization would have been 80 mg. One-tenth, or 8 mg., of standardized curare given

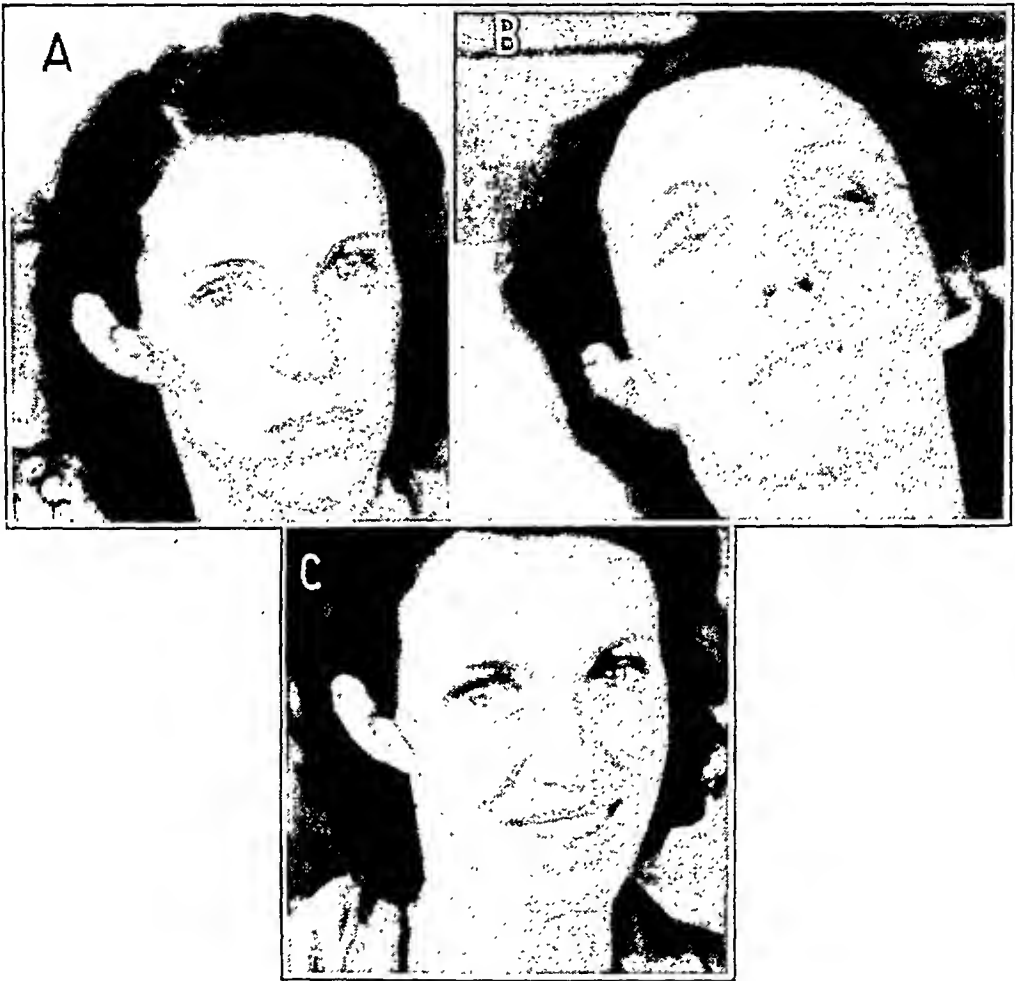


Fig. 1 (case 1).—*A*, myasthenic facies prior to injection of curare. *B*, appearance of patient (*A*) after injection of 7 mg. of standardized curare, showing complete external ophthalmoplegia and generalized paresis. *C*, relief of all effects of curare and symptoms of myasthenia by injection of prostigmine.

intravenously over a period of one minute produced a peak reaction two minutes later. There were marked exaggeration of symptoms, complete bilateral ptosis, pronounced dysarthria and weakness of the muscles of the neck and the extremities. Another test with 15 mg. of standardized curare produced profound generalized symptoms of myasthenia with respiratory embarrassment. Each test was terminated by injection of 1.5 mg. of prostigmine methylsulfate and $\frac{1}{100}$ grain of atropine

sulfate. The exaggerated effects of curare disappeared immediately, but the myasthenic symptoms remained the same.

Thyroidectomy was performed; the gland weighed 24 Gm. Unfortunately, pneumothorax developed, and the patient died thirty-six hours after operation.

The pathologic report by Dr. J. P. Tollman follows: "The tissue consisted of a rather thin fibrous stroma supporting lymphoid tissue. The lymphoid tissue showed numerous active secondary germinal centers in which mitosis was common. One or two thymic corpuscles were noted. There was no evidence of inflammation. Adipose tissue was rather abundant."

CASE 3.—C. M. L., a man aged 74, in 1939 began having attacks of diplopia at midday, which were relieved by a night's rest; bilateral ptosis appeared at about the same time, followed later by generalized fatigability and huskiness of the voice.

Examination about four months after the onset revealed bilateral ptosis; rapid fatigue of ocular movements could be produced, with almost complete external ophthalmoplegia and myasthenic facies, symptoms disabling to the patient.

Prostigmine Diagnostic Test.—Injection of 1.5 mg. of prostigmine methylsulfate resulted in a 4 plus score, with complete relief of all symptoms within ten minutes. For over two years this patient has been able to carry on full occupation. Oral use of prostigmine methylbromide gives complete symptomatic relief.

Curare Diagnostic Test.—The patient's weight, 140 pounds (63.5 Kg.), indicated that approximately 70 mg. of standardized curare was needed to produce partial curarization. Injection of one-tenth this dose, or 7 mg., of standardized curare intravenously produced complete bilateral ptosis, complete external ophthalmoplegia, weakness of the facial muscles and of the tongue, anarthria and generalized muscular paresis within one minute. At the peak of the reaction, within two minutes, the patient felt immobile and helpless. Prostigmine methylsulfate, 1.5 mg., was given intravenously. Within two minutes the effects of the curare and all myasthenic symptoms disappeared.

CASE 4.—E. E., a man aged 56, for one month prior to examination had noted drooping of the left eyelid at the end of the day and complete relief after a night's rest. The ptosis was gradually extending over longer periods each day.

Complete examination gave normal results except for slight ptosis of the right lid and more complete ptosis of the left lid. The patient's weight was 197 pounds (89.4 Kg.).

Curare Diagnostic Test.—Ten milligrams of standardized curare was given intravenously over a one minute period. Within two minutes a moderate degree of ptosis appeared on the right side and complete ptosis on the left, with bilateral weakness of the facial muscles typical of myasthenia; no other objective symptoms were noted. Prostigmine methylsulfate, 1.5 mg., given intravenously, rapidly cleared up the curare symptoms and all evidence of bilateral ptosis.

This patient presents a very early stage of myasthenia gravis and is being observed for further development of myasthenic symptoms before treatment is started. The specific response to the curare test, in our opinion, is conclusive evidence of myasthenia.

CASE 5.—Mrs. P. N., aged 37, in 1925 first noticed after swimming that her legs gave out while climbing a hill. Since that time there had been progressive weakness of both legs and arms. The fatigability was more noticeable after midday, but at times the patient would fall on mounting stairs or drop objects while carrying them. She had recently noted fatigue with reading and could read

better with one eye closed, but never had had diplopia or ptosis. Also, there was fatigue on chewing, but never dysarthria or dysphagia. All symptoms were relieved one week prior to and one week after menstruation. Dyspnea on exertion and postmalleolar edema were other complaints.

Examination.—Complete physical and neurologic examinations revealed nothing abnormal except for a slight suggestion of bilateral weakness of the facial muscles. No fatigability of ocular muscles could be elicited. Repeated muscular tests of the



Fig. 2 (case 5).—*A*, myasthenia, of twelve years' duration, the asthenia being limited to the extremities. *B*, appearance after injection of 5 mg. of standardized curare, showing complete ophthalmoplegia and generalized paresis. *C*, relief of all effects of curare and myasthenic symptoms by injection of prostigmine.

upper and lower extremities elicited subjective fatigability; electrical stimulation did not induce the Jolly reaction.

Curare Diagnostic Test.—The patient weighed 124 pounds (56.2 Kg.); 5 mg., or one-twelfth the physiologic dose, of standardized curare was given intra-

venously. Within one minute the patient showed bilateral ptosis, external ophthalmoplegia, facial weakness, dysarthria and complete flaccid paresis of the head and the upper and lower extremities. After two minutes 1.5 mg. of prostigmine methylsulfate with $\frac{1}{100}$ grain of atropine sulfate was given intravenously. Within two minutes all effects of curare and myasthenic symptoms disappeared.

Comment.—Patient 1 was severely disabled with myasthenia. Patient 2 had involvement almost limited to the ocular muscles in an unusual case of unilateral exophthalmos. Patient 3 had a mild form of the disease, which was completely controlled by prostigmine methylsulfate. Patients 1 and 3 gave strongly positive diagnostic reactions to prostigmine, but patient 2 gave an indifferent response and received no relief from any drug therapy. Patient 4 had a very early stage of myasthenia, for which the curare test enabled immediate diagnosis. Patient 5 presented an unusual case, since myasthenic symptoms extending over a twelve year period were confined to the larger muscles of the limbs and the shoulders, arms and legs, with practically no involvement of muscles of the oculomotor or the bulbar group. The curare test immediately brought out all the missing symptoms and clinched the diagnosis. After one-tenth the physiologic dose of curare, all 5 patients reacted specifically, with profound exaggeration of myasthenic symptoms, proof of the specificity of the active curare principle in the causation of the disease.

Technic of Curare Diagnostic Test.—About 1 mg. per kilogram of body weight of a standardized curare principle² administered intravenously produces mild generalized curarization in a normal adult. One-tenth this estimated physiologic dose is injected intravenously over a one minute period into the patient suspected of having myasthenia. Within two minutes after the injection the peak reaction occurs. If the patient has myasthenia, the existing myasthenic symptoms are aggravated, especially paralysis of the oculomotor muscles, weakness of the facial muscles and of the tongue, dysarthria and dysphagia. New symptoms may appear, such as flaccid paresis of the neck and extremities. The patient may be unable to speak or protrude the tongue and respiration of the diaphragmatic type may become labored. The test is to be terminated within two to three minutes by intravenous injection of 1.5 mg. of prostigmine methylsulfate with $\frac{1}{100}$ grain of atropine sulfate; within a minute all acute effects of curare disappear, and if the patient is reactive to prostigmine the myasthenia symptoms likewise disappear. Larger doses of standardized curare, up to one-fifth the physiologic dose, may be given but are unnecessary for diagnosis. Without the use of prostigmine the test would be dangerous. A physiologic dose of curare given to a patient with myasthenia gravis would probably be fatal unless artificial respiration was maintained or the antidote prostigmine administered.

SUMMARY

1. It appears that some failure in the action of acetylcholine exists in myasthenia gravis.
2. Physostigmine restores neuromuscular performance in most myasthenic patients.
3. Curare neutralizes acetylcholine action and produces artificial myasthenia gravis.
4. There is some evidence that a primary muscle disorder apart from neuromuscular block may occur in certain stages of the disease.
5. The myasthenic patient exhibits a pronounced sensitivity to curare. One-tenth the usual physiologic dose of curare produces profound exacerbation of existing symptoms, and generalized curarization adds new symptoms of myasthenia.
6. These phenomena suggest a specific diagnostic test for the disease. Injection of one-tenth the usual physiologic dose of standardized curare is a safe procedure if followed by administration of prostigmine methylsulfate. Larger doses must be administered with caution, as fatalities may occur.
7. Five patients with different phases of the myasthenic syndrome have shown a specific response to the curare diagnostic test, even though for some the prostigmine test was inconclusive.
8. The cause of myasthenia gravis should be found by explaining the occurrence in the disease of the neurophysiologic disturbance resembling chronic curarization.

607 Medical Arts Building.

DISTURBANCES IN PAROTID SECRETION IN AN UNUSUAL NEUROLOGIC SYNDROME

LOUIS LINN, M.D.
AND
LEO A. SPIEGEL, M.D.
NEW YORK

In this communication we wish to describe a method for measuring the disturbance in parotid secretion in an unusual syndrome involving the artery of the facial nerve—a branch of the anterior inferior cerebellar artery.

In 1901 Wallenberg¹ reported the case of a 70 year old man who had sudden loss of consciousness preceded by a brief period of tinnitus in the right ear and itching of the nose. The period of unconsciousness lasted twenty-four hours; on recovering the patient complained of vertigo. Neurologic examination revealed bilateral involvement of the sensory fifth nerve; paresis of the right motor fifth nerve; paralysis of the right sixth nerve; paralysis of the right seventh nerve, of peripheral type, and partial deafness, right eighth nerve. Pain and temperature sensations were diminished on the left side down to the second dorsal segment. There was slight hyperreflexia on the same side. The clinical diagnosis was hemorrhage from the ramus centralis arteriae radicularis nervi facialis dextri, a branch of the anterior inferior cerebellar artery. The patient lived seven years after his vascular insult. At necropsy the right side of the pons appeared much smaller than the left. Section revealed a hemorrhagic cyst in the tegmentum of the pons extending to the floor of the fourth ventricle. Caudally it reached the anterior end of the inferior olive and rostrally the lingula of the cerebellum. The cyst destroyed the motor nucleus, as well as part of the sensory nucleus and some of the sensory roots of the right fifth nerve. The nuclei of the sixth and seventh nerves on the right side were destroyed, as were the nuclei of Bechterew and Deiters, part of the restiform body, part of the posterior longitudinal bundle, the dorsal fibers of the cochlear nucleus as they passed to the trapezoid body and part of the spinothalamic and spinotectal tracts on the same side.

From the Neuropsychiatric Division of the Montefiore Hospital.

1. Wallenberg, A.: *Klinische Beiträge zur Diagnostik akuter Herderkrankungen des verlängerten Markes und der Brücke*, Deutsche Ztschr. f. Nervenhe. **19**: 227, 1901.

Wallenberg² expressed the belief that the extent of the lesion corresponded to the distribution of the branch of the anterior inferior cerebellar artery accompanying the right facial nerve, as was predicted clinically. Our own case resembled clinically the case just described.

REPORT OF A CASE

A white man, aged 46, a house painter for twenty years preceding his illness, had never suffered any symptoms that could be attributed to lead intoxication. The family and past history were noncontributory.

On Dec. 26, 1938, shortly after supper, he complained of a sudden lightning-like pain radiating from the left side of his face and head down the entire left side of the body. He did not lose consciousness but had to be carried to bed. He vomited for several hours thereafter. He felt numb and stiff over the entire left side of the body, although there were no paralyses. During the next few days he noticed that he could not close his right eye and that his mouth was pulled to the left. He also noted difficulty in chewing and speaking and a decided change in the quality of his voice. He experienced considerable dizziness, and a coarse tremor of his left hand, most pronounced on intention, developed. He was taken to a city hospital, where he remained for five months. During this time sensation on the left side of the body improved considerably and there was diminution of the tremor. All other symptoms remained essentially unchanged. Tarsorrhaphy was performed on the right side for iritis and keratoconjunctivitis. Shortly before admission to the Montefiore Hospital he complained of severe pain in one spot inside the left ear. In addition, he became aware of an intermittent whistling noise in the right ear.

Physical Examination.—Examination on admission gave essentially normal results. The blood pressure was 120 systolic and 90 diastolic. There was a tarsorrhaphy scar on the right side. The positive neurologic signs on admission were as follows:

1. A wide-based, conspicuously ataxic gait, with a tendency for the patient to fall in any direction.
2. Bilateral cerebellar signs, most noticeable on the the left, and a tendency to past pointing on the left.
3. Coarse tremor of the outstretched hand, most pronounced on the left and increased on intention.
4. Rhythmic myoclonus of the soft palate, pharynx and larynx, with a rate of 180 per minute.
5. Dysarthric, slurred, high-pitched, explosive speech.
6. Hyperactive tendon reflexes on the left; diminished left abdominal reflexes; no pathologic reflexes.
7. Hypalgesia, hypthermesthesia and hypesthesia over the entire left side of the body and face, with sparing of vibratory and position sensations.
8. Moderate inward deviation of the right eye and loss of lateral conjugate gaze in either direction; normal vertical gaze.
9. Vertical nystagmus on upward gaze.
10. Sluggishness of the left corneal reflex.

2. Wallenberg, A.: Anatomischer Befund in einem als Blutung in die rechte Brückenhälfte, etc. aus dem Ramus centralis arteria radicularis nervi facialis dextri geschilderten Falle, Deutsche Ztschr. f. Nervenhe. 26:436, 1904.

11. Diminution in superficial sensation over the left side of the face and the anterior wall of the external auditory canal.
12. Complete lower motor neuron paralysis of the right seventh nerve.
13. Bilateral partial nerve deafness, most noticeable on the right.
14. Bilateral absence of labyrinthine response to Bárány test.
15. Bilaterally diminished palatal and pharyngeal reflexes, the responses on the right being more sluggish than those on the left.
16. Questionable weakness of the right motor fifth nerve, and fibrillations of the tongue.
17. Moderate arteriosclerosis of the retinal vessels.

Laboratory Data.—The results of all laboratory studies were within normal limits. The spinal fluid showed an initial pressure of 115 mm. There were 5 lymphocytes per cubic millimeter, and the protein was 37 mg. per hundred cubic centimeters.

Subsequent Course.—In the five months which has elapsed since the patient's admission to the hospital involvement of the right motor fifth nerve has become definite. In addition, myoclonic movements of the diaphragm have been recently observed fluoroscopically. The neurologic status has otherwise remained the same.

It is evident that the involvement of the cranial nerves in our case was practically identical with that observed by Wallenberg in his case. In addition, there were hyperreflexia on the left side and similar sensory dysfunction in the 2 cases. Cerebellar involvement was plainly evident in our case and was probably present in Wallenberg's case, although his description does not make this certain. Inasmuch as the lesion in Wallenberg's case involved the central tegmental tract, palatal myoclonus should have been present, as in our case, although it was not mentioned.

Several investigators have pointed out³ that the motor secretory nucleus of the parotid gland, the inferior salivatory nucleus, is located in the region covered by the lesion observed in Wallenberg's case. Inasmuch as we felt that the lesion in our case closely resembled in its anatomic relation that observed in Wallenberg's case, a disturbance in parotid secretion on the right side was anticipated.⁴ Studies of parotid secretion on this patient were accordingly begun.

STUDY ON PAROTID SECRETION

Method.—Measurements of parotid flow were made by the Strongin parotid secretory disk.⁵ This instrument consists of two metal cups, one soldered within

3. Kohnstamm, O., and Wolfstein, D. J.: Versuch einer physiologischen Anatomie des Vagusursprung und des Kopfsympatheticus, J. f. Psychol. u. Neurol. 8:177, 1907. Yagita, K., and Hyama, S.: Ueber das Speichelsekretioncentrum. Neurol. Centralbl. 28:738, 1909. Feiling, A.: On the Bulbar Nuclei with Reference to the Existence of a Salivatory Center in Man, Brain 36:255, 1913.

4. Dr. Otto Marburg suggested the possibility of such a condition and guided us in the preparation of this report.

5. Dr. E. Strongin gave us the use of his disks and his technical advice. The actual disk is about the size of a dime.

the other. The disk is placed over the papilla of Stensen's duct so that the papilla lies entirely within the inner cup. With a little practice and with good lighting this is easily performed. The disk is held in position against the buccal mucosa with one hand. The operator then makes suction on tube *B*. This creates a vacuum in the space between the inner cup (*C*) and the outer cup (*A*), which secures the disk in its proper position. A small pinch clamp is then placed on tube *B*. Relatively little suction on tube *B* is necessary to produce the required vacuum. Under no circumstances should the subject experience pain or discomfort due to the suction. The pinch clamp can then be secured to the subject's clothing by means of a safety pin. The outlet from the inner cup is connected with a 1 cm. pipet (*D*) calibrated in hundredths of a cubic centimeter. The length of the tubing used in establishing this connection does not matter. Before the connection is made a droplet of water is placed within the pipet. It is the movement of this droplet that is recorded.

It is desirable to conduct these measurements in a soundproof room, since extraneous stimuli may produce alterations in the parotid flow. It is preferable that the subject have had no medication for the preceding forty-eight hours. Studies should be made in the morning. The subject omits breakfast and is not permitted to smoke. The procedure is explained to him in simple terms, and every effort is

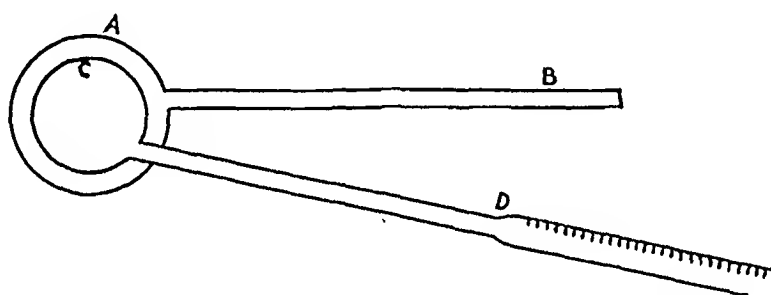


Diagram of the Strongin parotid secretory disk.

made to set him at his ease. He is instructed to sit back comfortably in his chair with his eyes open. He should not fall asleep during the experiment and should not read or engage in other mental activity.

When the disk is properly placed, movement of the water droplet in the pipet is almost immediately evident. (There may be a latent interval of psychic inhibition of parotid secretion, lasting several minutes.) The position of the disk can be rapidly checked by putting a drop of lemon juice on the subject's tongue. This procedure will be followed by an almost instantaneous spurt of the water droplet. A dropper bottle containing lemon juice is made available for this purpose. After this procedure at least six minutes must elapse before measurements are made. They are carried out as follows: The subject is instructed to swallow once and then to swallow no more until told to do so. In the event that he swallows before he is instructed to do so, he must signify this fact by raising his hand. Measurements must then be started all over again, beginning with this swallow. The flow during the first minute following the swallow is discarded. Readings of the position of the droplet are then made every minute for five minutes, at which time the patient is ordered to swallow. The procedure is then repeated. For most accurate determination of the resting secretory rate six such intervals should be recorded. The pipet must be chemically clean and perfectly dry.

Results.—The resting secretory rates recorded on Feb. 27, 1942 follow.

Readings, Cc.	
Left	Right
0.930	0.910
0.855	0.905
0.812	0.901
0.732	0.900
0.680	0.895
0.600	0.889
<hr/>	
Total secretion 0.33	0.02
0.535	0.886
0.482	0.884
0.425	0.882
0.350	0.875
0.302	0.873
0.255	0.871
<hr/>	
Total secretion 0.28	0.02
0.960	0.869
0.900	0.867
0.855	0.862
0.790	0.859
0.735	0.852
0.680	0.850
<hr/>	
Total secretion 0.28	0.02

Stimulation with lemon juice produced spurts of parotid secretion on the left side, but not on the right, even when the right side of the tongue was stimulated directly. (Ordinarily, stimulation of the right side of the tongue produces a primarily ipsilateral parotid response, and vice versa.)

On injection of $\frac{1}{80}$ grain (8 mg.) of pilocarpine hydrochloride hypodermically the following results were obtained:

Readings, Cc.	
Left	Right
0.860	0.845
0.810	0.842
0.730	0.841
0.625	0.835
0.555	0.830
0.470	0.820
<hr/>	
Total secretion 0.49	0.02

Readings, Cc.— <i>Cont.</i>		
	Left	Right
	0.370	0.807
	0.300	0.788
	0.230	0.765
	0.150	0.730
	0.070	0.690
	0.010	0.640
	<hr/>	<hr/>
Total secretion	0.36	0.17
	0.920	0.575
	0.800	0.500
	0.710	0.425
	0.600	0.350
	0.480	0.268
	0.375	0.185
	<hr/>	<hr/>
Total secretion	0.55	0.39
	0.940	0.812
	0.820	0.732
	0.625	0.662
	0.500	0.580
	0.350	0.510
	0.200	0.435
	<hr/>	<hr/>
Total secretion	0.74	0.38

It should be noted that the increase in secretion on the right side set in six minutes after the injection of pilocarpine. This time interval was noted by Strongin⁶ in a large series of cases of non-neurologic conditions with a high degree of regularity. There seemed to be somewhat of a lag in the response to pilocarpine on the left side. However, at the termination of the experiment the left side again far outstripped the right in rate of secretion.

Repetition of the experiment on May 28 gave the following results:

Readings, Cc.		
	Left	Right
	0.900	0.810
	0.800	0.810
	0.660	0.810
	0.540	0.810
	0.410	0.810
	0.300	0.810
	<hr/>	<hr/>
Total secretion	0.60	0.00

6. Personal communication to the authors.

When lemon juice was placed on the tongue the response was as follows :

Readings, Cc.	
Left	Right
0.900	0.772
0.790	0.772
0.650	0.772
0.480	0.772
0.370	0.772
0.260	0.772
<hr/>	
Total secretion 0.64	0.00

It should be noted that on this day there was total absence of secretion on the right, which was associated with a much higher rate of resting secretion on the left than was observed in the previous experiment. It should also be noted that there was once more no response to lemon juice on the right. That this was not an artefact due to improper placement of the disk is clear from the following figures, obtained after the injection of $\frac{1}{40}$ grain (16 mg.) of pilocarpine hydrochloride. It should be emphasized that there was no alteration in the position of the disk during this experiment.

Readings, Cc.	
Left	Right
0.980	0.755
0.890	0.755
0.800	0.715
0.540	0.480
0.400	0.190
<hr/>	
Total secretion 0.58	0.57

Although further measurements were not recorded, it can be stated that a profuse parotid flow was observed bilaterally in response to pilocarpine. This proves that the previously noted absence of resting secretion and absence of response to lemon were not artefacts.

COMMENT

It is to be observed that the left parotid gland maintained a resting secretory rate which was considerably higher than that on the right; that whereas the left parotid gland responded to both lemon and pilocarpine, the right gland responded only to pilocarpine. It would seem, then, that since the reflex between the taste buds and the parotid gland was destroyed on the right side, pilocarpine acts directly on the parotid gland. Our results also seem to indicate that the motor nerves of the parotid gland do not have bilateral representation in the brain stem, as was suggested by Kohnstamm on the basis of animal experimentation. The mechanism of the compensatory increase in secretion on the side opposite the lesion is speculative. It is possible that this

increase represents a release phenomenon due to the destruction of contralateral supranuclear autonomic pathways. The anticipated hypersensitivity of the denervated right parotid gland to pilocarpine, in accordance with Cannon's law of denervation, was not observed.

The Strongin technic thus afforded a precise method for demonstrating the anticipated disturbance in parotid secretion in this patient. It permitted the elucidation of the nature of this disturbance and the nature of the action of the pilocarpine on parotid secretion. The method is presented in detail in the belief that it provides a useful tool in conducting a clinical neurologic examination, which may be as valuable in other cases as it proved to be in ours.

Montefiore Hospital.

TREATMENT OF POST-LUMBAR-PUNCTURE HEADACHE WITH ERGOTAMINE TARTRATE

SAMUEL A. GUTTMAN, PH.D., M.D.

NEW YORK

The object of this paper is to summarize some observations on the treatment of post-lumbar-puncture headache, following spinal anesthesia, with ergotamine tartrate.

The use of ergotamine tartrate for the treatment of post-lumbar-puncture headache was mentioned by Targowla and Lamache.¹ They reported that ergotamine tartrate seemed to be of value in the treatment of post-lumbar-puncture phenomena. Lennox, von Storch and Solomon² reported on the effect of ergotamine tartrate on nonmigrainous headache. In their series of patients who were unsuccessfully treated for many types of headache other than migraine were 7 who had headaches and a decreased cerebrospinal fluid pressure after lumbar puncture.

PRESENT INVESTIGATIONS

The 35 patients who were treated with ergotamine tartrate were from a group of 418 patients on whom lumbar puncture was performed and spinal anesthesia induced (with procaine). Most of the patients who received the drug were not allowed out of bed because of some recent operative procedure. They were permitted to remain in any position in bed directly after receiving the ergotamine tartrate. All the patients elected to lie flat in bed. After varying lengths of time following the administration of the drug—from five minutes to two hours—they were allowed to sit up with the head of the bed elevated 50 degrees or more. The effect of having the head of the bed raised was observed and recorded for each patient. The approximate elevation, in degrees, and the time of onset and the character of the symptoms were noted. These data served as a base line for determining the effect of ergotamine tartrate. Some patients, those who received the drug by vein, had the head of the bed raised as often as every five to ten minutes in order that the effect of the drug might be determined.

It is not possible to demonstrate conclusively that headache following the induction of spinal anesthesia is totally independent of the anesthetic agent used, but

From the Jewish Hospital, Philadelphia.

Ergotamine tartrate (gynergen) was supplied by Sandoz Chemical Works, Inc., New York.

1. Targowla, R., and Lamache, A.: *Les accidents de la ponction lombaire et leur traitement*, *Ann. de méd.* **22**:345, 1927.

2. Lennox, W. G.; von Storch, T. J. C., and Solomon, P.: *The Effect of Ergotamine Tartrate on Non-Migrainous Headaches*, *Am. J. M. Sc.* **192**:57, 1936.

clinical observations do not indicate any difference in signs or symptoms and this type of headache seems to be identical with the post-lumbar-puncture headache.

Ergotamine tartrate (gynergen) was given to 35 patients who had post-lumbar-puncture headache following spinal anesthesia.

Ergotamine tartrate is a potent drug. The dose is that amount which is sufficient to produce the desired effect in a particular patient. One patient may be able to tolerate as much as 1 mg. given parenterally within several hours and show no minor toxic symptoms, while another may exhibit toxic phenomena after receiving 0.25 mg. The drug was usually administered parenterally—frequently by vein, usually by deep subcutaneous or muscular injection. In some instances the drug was administered sublingually.

For parenteral administration the following method was found to be fairly satisfactory. The patient was given from 0.25 to 0.50 mg. of ergotamine tartrate into the deltoid region. One of several things occurred during the next two hours.

Effect of Ergotamine Tartrate on Post-Lumbar-Puncture Headache

	No. of Patients	Percentage
Patients treated.....	35	100.0
Result of treatment		
Relief.....	29	82.9
Some relief.....	2	5.7
No relief.....	4	11.4

1. The patient was able to sit up or walk about, if ambulatory, free of a headache or with but a very slight ache. For about two to three tenths of the patients one dose was sufficient and the headache did not return. It is now deemed advisable to give a patient the same dose two or three times a day for about two days to ward off any recurrence. When the headache was relieved and then returned, the recurrence was from four to twelve hours after the drug was administered.

2. The patient was relieved and could be up without a headache, but some of the minor toxic symptoms, e. g., loss of appetite, nausea, vomiting and various vasospastic phenomena, occurred. The patient responded favorably to the drug, but the therapeutic dose had been exceeded. Subsequent doses for such patients should be between one-half to two-thirds the initial dose, so that minor toxic symptoms do not recur.

3. The patient was not improved, and no minor toxic symptoms appeared. When this occurred, either a therapeutic dose had been administered and the patient did not obtain relief from the drug or a therapeutic dose had not been given. To these patients a 0.25 mg. dose was administered every two to three hours until he was able to be up

without a headache or there was no change in the intensity of the headache and minor toxic symptoms appeared. The drug is not supposed to be given in excess of 1 mg. (parenterally) in twenty-four hours. However, it has been noted that some patients can be given as much as 2 mg. in twenty-four hours for several days without the appearance of minor toxic symptoms. In general 1 mg. should be the maximum amount for twenty-four hours.

4. The patient exhibited minor toxic symptoms with no relief from the headache. The dose was repeated in twelve hours, and if the same result occurred it was deemed that the patient derived no benefit from ergotamine tartrate.

Ergotamine tartrate was administered by the intravenous route to 8 patients. Each person received 1 cc. of physiologic solution of sodium chloride by vein about two hours before ergotamine tartrate was administered, and in no instance was relief afforded by the injection of the saline solution. After injection of 0.25-0.50 mg. of ergotamine tartrate by vein the patients reported beginning relief from the headache in fifteen to thirty minutes. These patients were usually made to sit up each five to ten minutes, and by the end of a half-hour the headache was entirely gone or greatly diminished in intensity. This method was employed to demonstrate the precise response to intravenous administration, and it may be used in treating patients with severe headache or as a final measure in attempting to treat that group who do not seem to respond to ergotamine tartrate.

Ergotamine tartrate, at least according to these data, is of value in relieving post-lumbar-puncture headache in eight to nine tenths of the patients only when the drug is administered according to the tolerance of the particular patient for the drug. Each person differs in this respect, and one must administer the drug as carefully as one rapidly digitalizes a patient or as one administers morphine sulfate to a patient with acute myocardial infarction. The dose for a particular patient is that amount of the drug which gives the desired therapeutic effect. Once the dose for a patient is determined it is advisable and practical to employ this quantity or to reduce it to the minimal therapeutic dose.

710 West One Hundred and Sixty-Eighth Street.

JUVENILE AMAUROTIC IDIOCY

A CLINICOPATHOLOGIC STUDY

ALBERT J. LUBIN, M.D.*

SAN FRANCISCO

AND

OTTO MARBURG, M.D.

NEW YORK

Clinicopathologic studies of the juvenile type of amaurotic family idiocy are infrequent. The present case offers an opportunity to correlate the neurologic, psychologic and electroencephalographic studies made shortly before the patient's death with the pathologic observations.

REPORT OF A CASE

A 16 year old youth entered the hospital Nov. 1, 1940 with the complaint of blindness for ten years, loss of memory and convulsions for one year. His development was said to have been normal until he was 6 years old. There was no family history of any neurologic or psychiatric disorder. His mother, father and 20 year old brother were alive and well.

At the age of 6 years his mother noticed that he started to bump into objects, and soon after beginning school his first grade teacher noted difficulties in vision. An ophthalmologist told the parents that the condition would progress to complete blindness. During the following two years he lost all vision in both eyes save light perception. He was enrolled in a school for the blind when he was 8 years old. He disliked the school, was resentful of his blindness and failed to learn to read Braille. From the age of 11 to 15 years he was kept in a private school; he is said to have done satisfactory school work and to have become socially adjusted. In October 1939 he began to have convulsive seizures of the grand mal type; at first they occurred once or twice each week but subsequently increased in frequency to once every two or three days. They sometimes occurred in groups with repeated seizures during a single day.

Physical Examination.—Nothing abnormal was noted except in the neurologic and ophthalmoscopic examinations. His gait was moderately ataxic. The Romberg sign was positive. There was some dysmetria in all extremities. All of his movements were rather slow. There was generalized hypotonia, though he was not particularly weak. An occasional choreiform movement was noted. Of the deep reflexes of the upper extremity only the left biceps was elicitable, and it was weak. The knee jerks were difficult to obtain, but the ankle jerks were brisk. The abdominal reflexes were sluggish. The big toes were maintained in a con-

* Fellow of the Rockefeller Foundation, 1941-1942.

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From the Neurological Institute of New York, the Department of Neurology of the Columbia University College of Physicians and Surgeons, and the Division of Neuropsychiatry of the Stanford University School of Medicine.

stant state of dorsiflexion; no pathologic reflexes were elicited. All types of superficial and deep sensation were intact. Only light perception was present in both eyes. The optic disks were flat and yellowish; all retinal vessels were extremely narrow. Small spicules of pigment were scattered over the entire surface of the fundus, only a few being present, however, at the macular area or around the disk. Both lateral and vertical nystagmus were present and were greatly accentuated after the air encephalogram was taken. No evidence of involvement of other cranial nerves was noted.

Mental Examination.—The boy was ordinarily cooperative, although he had an occasional temper tantrum. His mood was rather indifferent. He spoke volubly. Sometimes, however, he merely repeated "yes" over and over again, explaining that the nurses were asking him whether he could see. There was no other evidence of hallucinations or delusions. He knew the date of the month but was unable to state where he was or to give the name of the president. His memory was poor, and his judgment was greatly impaired. The psychometric report by Dr. Ann Magaret follows:

"Classification: The patient is mentally deficient (probably an imbecile).

"Test Results: The revised Stanford-Binet test form L gave a mental age between 6 and 7 years. The average grade level with the Lowe-Shimberg scaled information test was below the fourth, probably at the second. The average mental age was below 9 years, probably 6 years.

"Analysis of Test Results: Interpretation of these results should be made with caution, since Donald is blind and could be given only such verbal tests as could be presented orally. None of the concrete performance tests was applicable. His general vocabulary on the Stanford-Binet list is at the 8 year level. On tests of immediate memory he falls at the 5 year level, and on tests of general comprehension, at the 8 year level. His fund of general information is that which would be expected from a second grade pupil. His ability to succeed with some information items at recognition, when he had failed to recall them, suggests that he may have known many of the questions at some time in the past, although he is today unable to answer them.

"Comment: Donald is a hesitant, uncertain but friendly and cooperative boy, who seems to exert a tremendous amount of effort in the test situation. He is cheerful and talkative, asks numerous questions about the materials used for the test and volunteers much information about the schools he has attended and the doctors he has seen.

"His attack on the test items is delayed and somewhat erratic. Frequently he succeeds with numerous subtests on a given item, only to fail on the crucial one, and hence lose all credit. He gives the impression of having to search long for his answers; his responses are slow, poorly phrased and uncertain. He stutters markedly when he is blocked on a question and always gropes for the proper words to express his answers. Nevertheless, he seems able to maintain his attention for unusually long periods. He seldom asks for repetition of instruction. He is often blocked in recalling names of simple objects; he struggled long to remember the word 'grass,' and finally asked in desperation, 'What do you call that stuff in the back yard?'

"Impression: The general impression is that of a cheerful, friendly, cooperative but hesitant and uncertain boy of imbecile grade intelligence. The wide discrepancy between his performance on vocabulary and on immediate memory items; his blockings on many of the questions; his ability to succeed with items on a recognition level when he has failed to recall them, and his general delay

and retardation in his test behavior, all are in agreement with the diagnosis of mental deterioration, which seems unquestionable in view of the earlier test results (intelligence quotient 133 at the age of 3 to 6 years)."

Laboratory Data.—The blood count and urinalysis revealed nothing abnormal. The sedimentation rate was 8 mm. per hour. The spinal fluid was normal: The Pandy reaction was negative, the total protein 22 mg. per hundred cubic centimeters and the colloidal gold curve 1112100000. The Wassermann reaction was negative for both the blood and the spinal fluid. The spinal fluid pressure was elevated, being over 300 mm. of water with the patient in a horizontal position. Flat roentgenograms of the skull were normal.

Electroencephalogram: Eight to 9 per second waves were revealed in all areas (Nov. 2, 1940). A small amount of random slow activity was present, being greatest in the occipital leads (fig. 1). None of this slow activity was of great amplitude, the maximum being 50 microvolts.

Air Encephalogram: On November 4, Dr. R. R. Newell reported: "The ventricular system is of rather large volume (fig. 2). In the left temporo-occipital region there is a superficial channel which seems somewhat increased in size. There are a few channels on the mesial surfaces of the hemispheres, but elsewhere the subarachnoid channels are scanty or wanting."

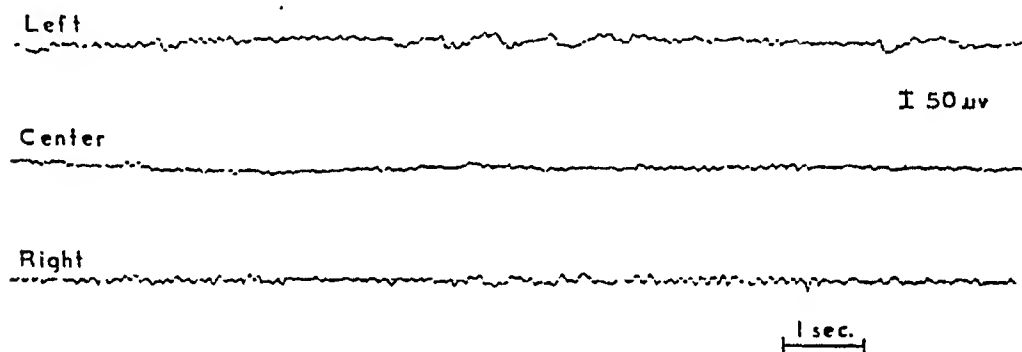


Fig. 1.—Electroencephalogram from the occipital region. Some slow random waves of low amplitude are present on the left side. The alpha rhythm is usually 8 to 9 per second.

Course.—A diagnosis of amaurotic family idiocy of the juvenile type was made. The patient was admitted to the Napa State Hospital, Imola, Calif., on November 26. A report from there stated that he was agreeable, childish, asked many questions, but wanted to go home. He ate and slept well. His speech remained relevant and coherent until his terminal pneumonia. He died Jan. 6, 1941. Dr. I. E. Charlesworth, the medical superintendent of Napa State Hospital, permitted us to examine the brain.

Macroscopic Examination.—The brain appeared to be larger than normal; it weighed 1,450 Gm. The sulci were shallow.

Microscopic Examination.—The characteristic cellular changes of amaurotic family idiocy were observed in the vast majority of the ganglion cells that were examined. These changes were most evident in the cerebral cortex and least so in the caudal end of the medulla. Most of the cells were swollen and appeared to be ballooned or saclike (fig. 3). The Nissl substance had more or less disappeared; it was rarely seen in the cortex. Neurofibrils were not definitely observed in many of the cells stained by the Bielschowsky or the Bodian method; in others

the neurofibrils were pushed to the periphery, sometimes causing the cell wall to appear thickened (fig. 3 *C*). The nucleus was usually at the periphery of the cell or in the base of one of the dendrites (fig. 3 *B*). Its wall was often hyperchromatic. Occasionally it appeared to have burst, and its contents lay free in the cytoplasm. The cytoplasm was usually filled with granules. In sections stained with cresyl violet



Fig. 2.—Air encephalogram. Except for a rather large superficial channel on the left and a few other channels at the mesial surface, no air has entered the subarachnoid space.

these granules were yellow. With scarlet red they were either yellow or yellow-orange; no bright red granules were observed with this method. Hematoxylinophilic granules appeared in only a few cells in sections stained with the Schaffer method. Mingled with the large cells were some that were smaller and appar-

ently shrunken. Others appeared to be shadow forms, with absence of nuclei and pale pigment. There was disappearance of cells, especially in the cortex; a resultant area of status spongiosus was occasionally seen.

Sections from the frontal lobe, including the frontal pole, the motor area, the premotor area and the gyrus rectus, showed pronounced diminution in the number of cells in all layers, especially in the third and fifth (figs. 4 and 5).

In the first, second and third temporal convolutions and in Heschl's convolution diminution in the number of cells was not as marked as in the frontal region, in spite of severe alterations in individual ones (fig. 6). Cell-free patches, how-

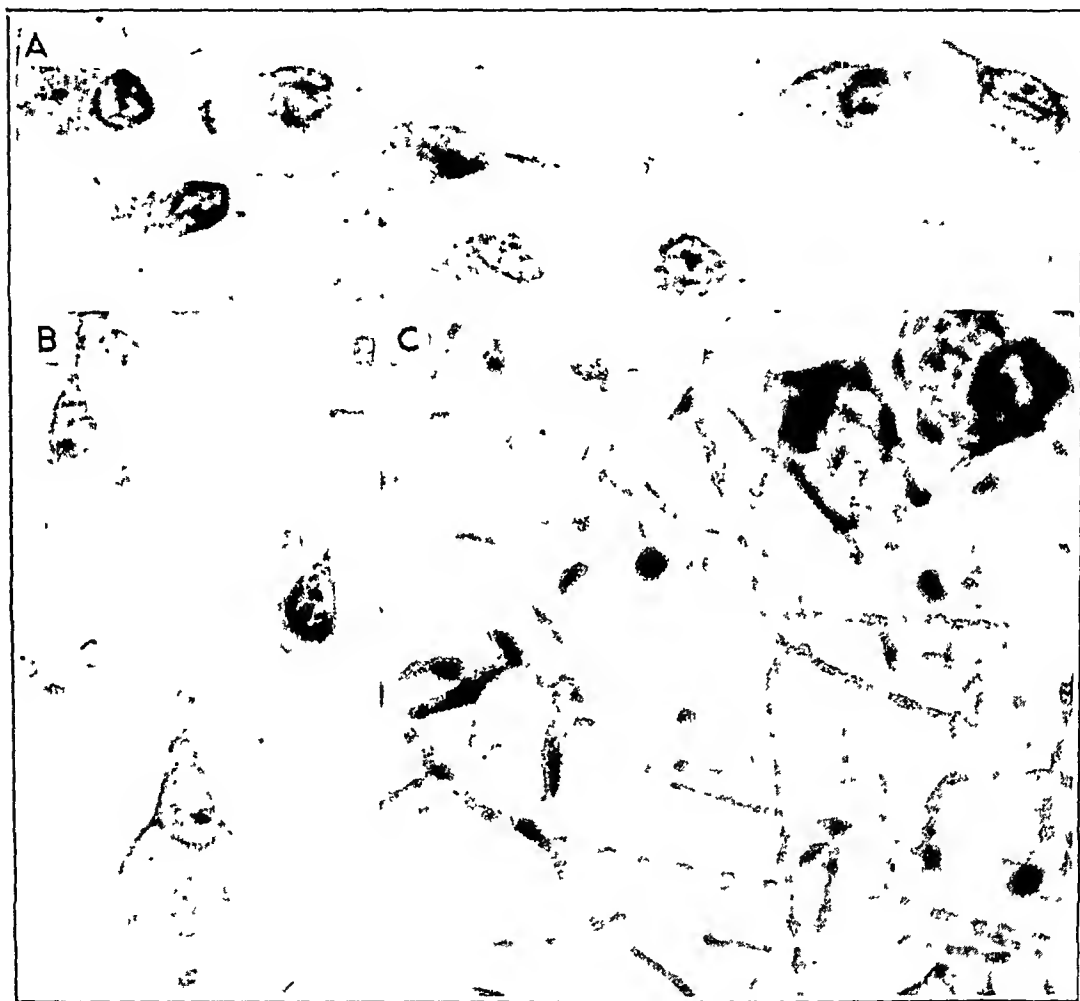


Fig. 3.—*A*, swollen spindle cells in the sixth layer of the cortex. Cresyl violet stain. *B*, pear-shaped cell in the lower portion of the third layer. The nucleus is pushed into the apical dendrite. The cytoplasm is filled with pigment. Cresyl violet stain. *C*, ballooned cells in the fifth layer. The nuclei and neurofibrils are at the periphery. Bodian stain.

ever, were present and were most evident in the third layer. Loss of cells in all layers was also noted in the posterior central gyrus, the superior parietal lobe, the supramarginal gyrus and the angular gyrus of the parietal lobe (fig. 7). Similar to that in the temporal region, this loss was not as great as in the frontal lobe. The number of cells was almost normal in the gyrus cinguli. There was no decrease in the number of cells in the gyrus hippocampi and the cornu ammonis.

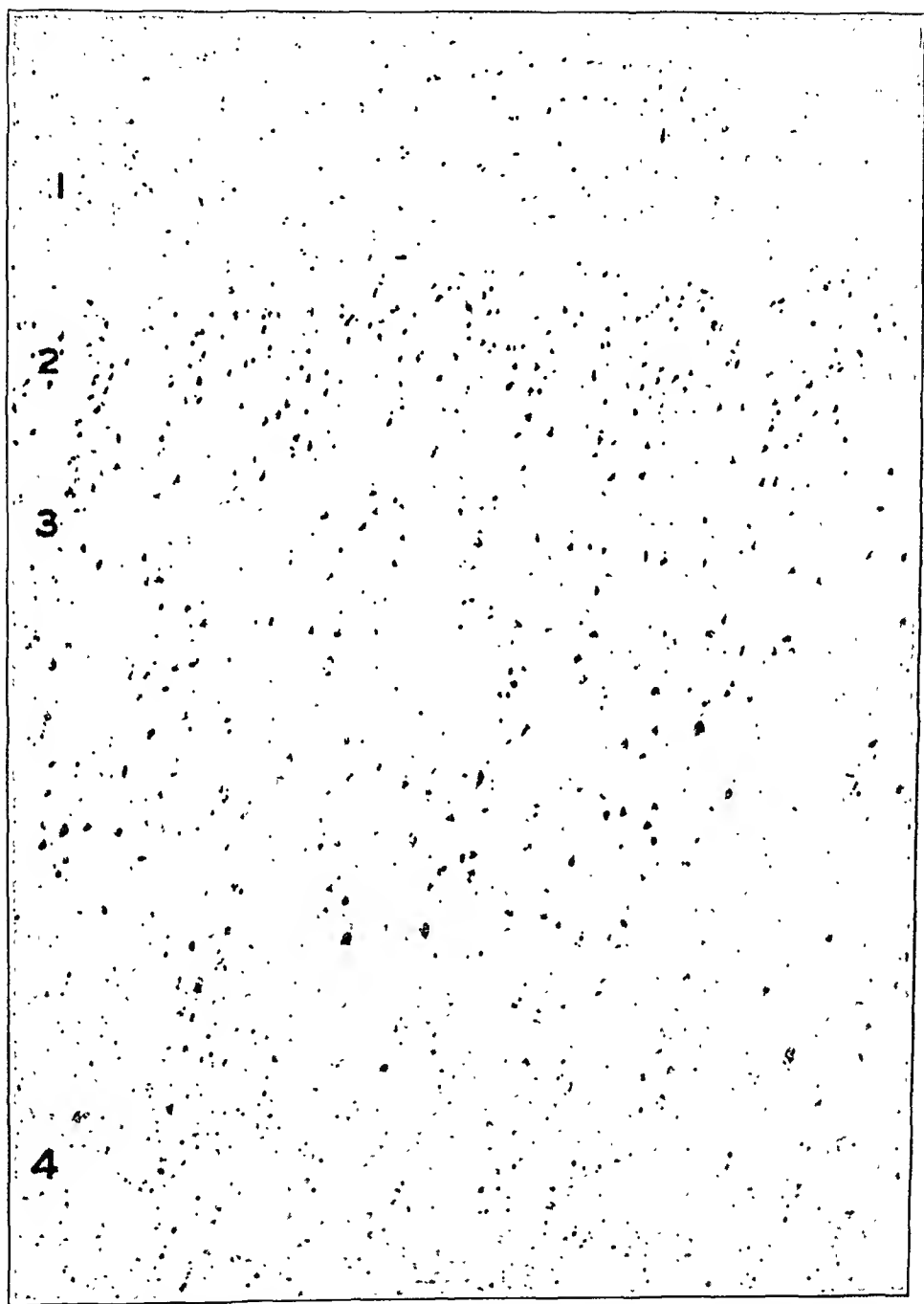


Fig. 4.—Frontopolar region. Many cell gaps are present, especially in the third layer. Cresyl violet stain.

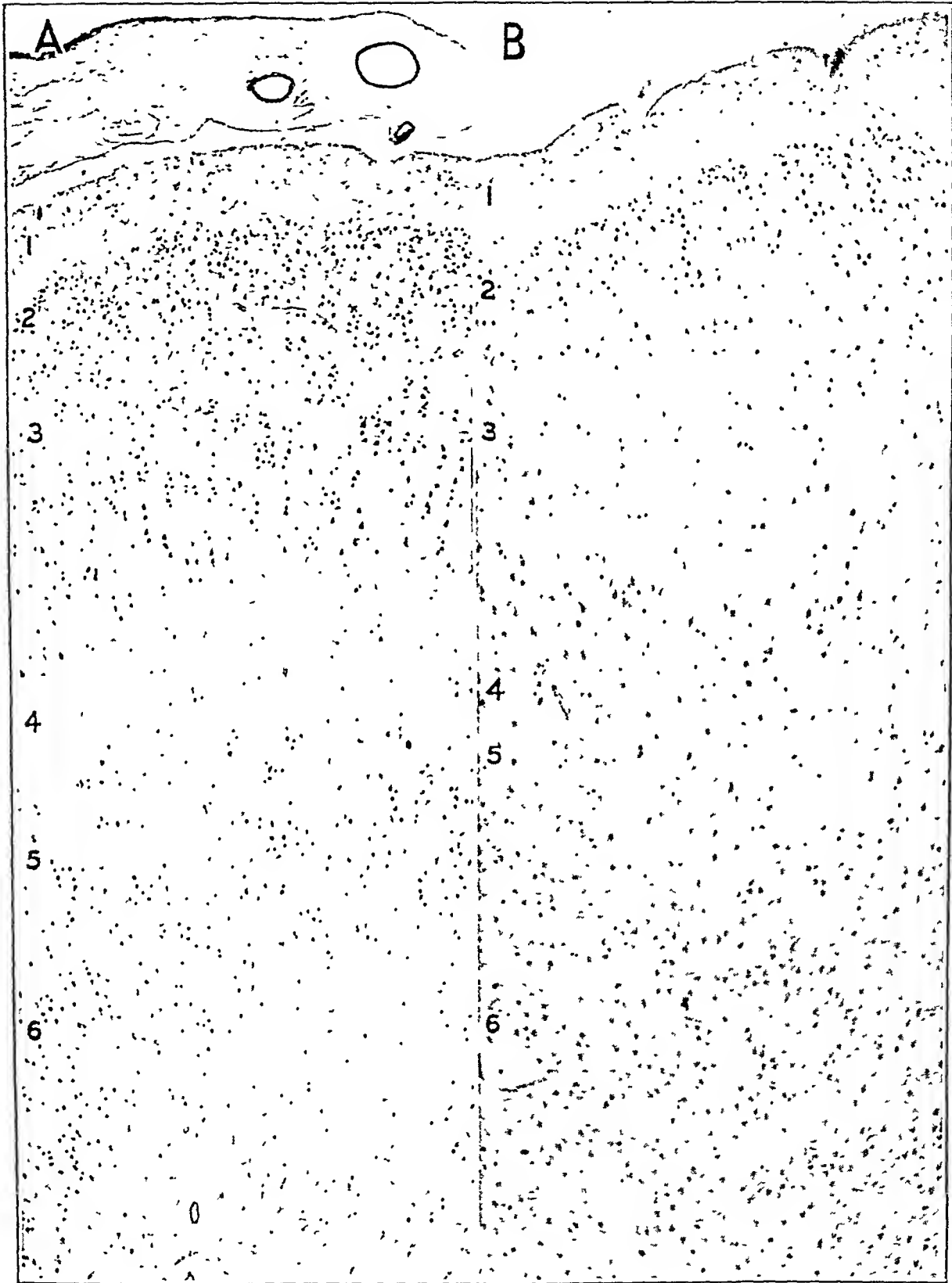


Fig. 5.—*A*, middle occipital gyrus; *B*, superior part of motor area, frontal lobe. Loss of cells is much more pronounced in the frontal than in the occipital lobe. The giant pyramidal cells are absent. The pia-arachnoid in *A* is thickened and contains many histiocytes. Cresyl violet stain.

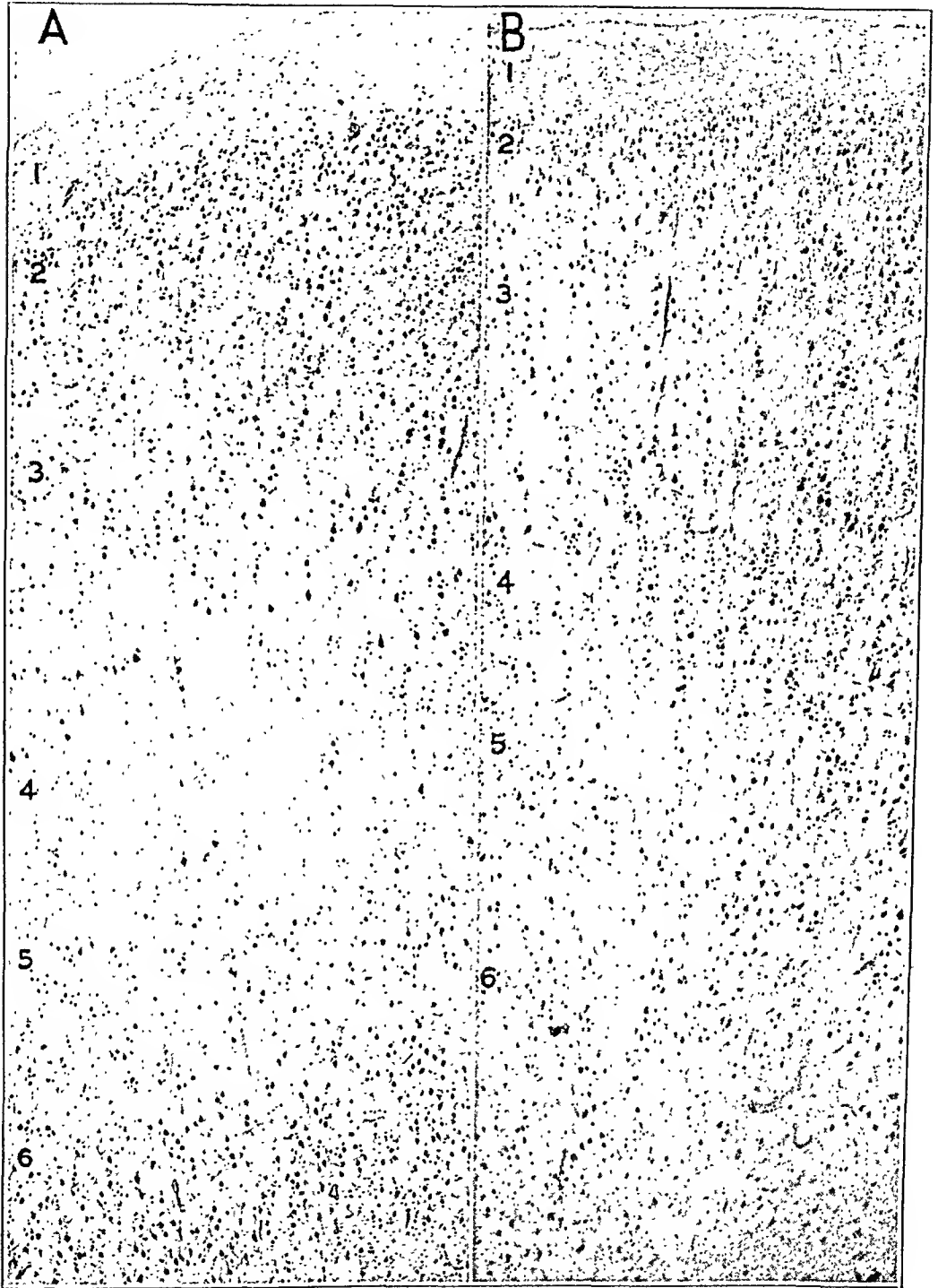


Fig. 6.—*A*, second, and, *B*, third temporal gyrus. Cellfree patches are especially evident in the third and fifth layers. Cresyl violet stain.

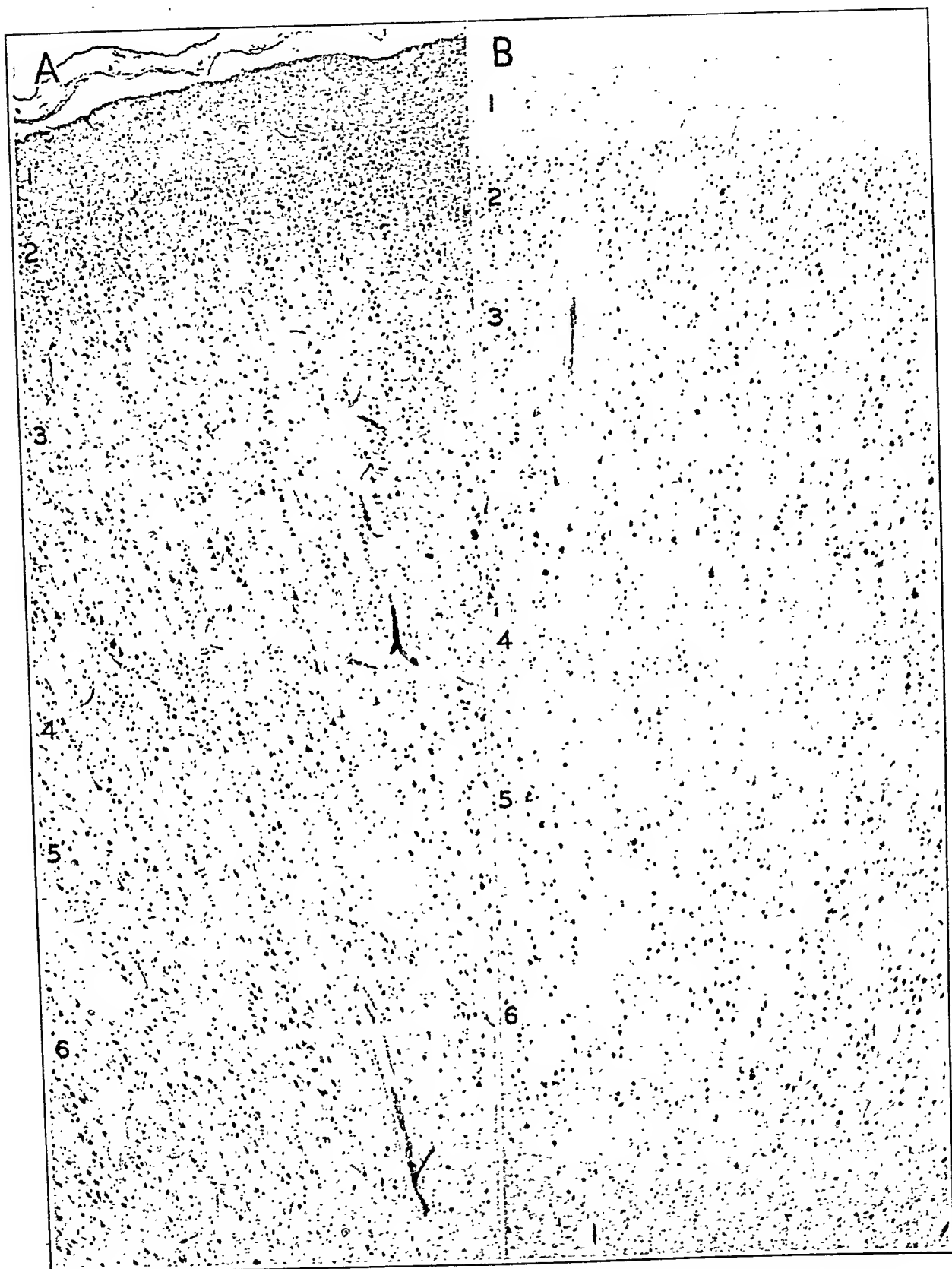


Fig. 7.—*A*, supramarginal gyrus; *B*, superior parietal lobe. The cell loss is similar to that in the temporal lobe.



Fig. 8.—Cornu ammonis. All of the large cells are swollen; those in the fascia dentata are of normal size. Cresyl violet stain.

However, all of the large cells of the cornu ammonis were affected. Most of the smaller ones in the fascia dentata appeared to be normal (fig. 8). In the subiculum some of the cells were normal in both shape and size. Sections from the occipital lobe, including the area striata and the medial and superior occipital gyri, appeared to have the least diminution in the number of cells (fig. 5); in fact, the number sometimes appeared to be normal. The molecular layer contained numerous swollen astrocytes in all parts of the cortex that were examined. Horizontal cells of Cajal were occasionally seen in this layer; they seemed to be degenerating. The radial fibers and the bands of Baillarger were present in all areas examined. The superficial tangential plexus was absent. The number of fibers in the interradiate and superradiate networks was also diminished. This diminution was least prominent in the occipital lobe. Swelling of the glia cells similar to that seen in the ganglion cells was frequently observed. Granules were seen in their cytoplasm, and occasionally the nucleus was homogeneous or degenerated. Neuronophagia was noted occasionally.

Similar types of cell degeneration were observed in the basal ganglia, midbrain, pons, medulla and cerebellum. The lower portion of the medulla appeared to be relatively least affected; some of the large ganglion cells retained their normal appearance and distribution of Nissl substance. No demyelination was present in Pal-Weigert sections. In the cerebellum, most of the Purkinje cells were absent. Those remaining were swollen. Bergmann's glia cells were increased in number. Many of the cells in the granular layer were pale and swollen; some contained vacuoles. The spinal cord was not examined.

The pia-arachnoid was thicker than usual (fig. 5 A). There was an increase in the number of fibroblasts, and many of them were swollen. Histiocytes containing granules were also observed.

COMMENT

The disorder in this case was typical of the juvenile form of amaurotic family idiocy from both the clinical and the pathologic aspect. The photographic similarity among cases mentioned by Sjögren¹ was present, namely: (1) initial onset of visual disturbances between the fifth and the eighth year, progressing to total blindness in one or two years, with retinitis pigmentosa and optic nerve atrophy; (2) mental deterioration and behavior disturbances, progressing throughout the course of the disease; (3) convulsions, usually beginning fairly late; (4) other neurologic manifestations, such as ataxia, tremors, nystagmus and pathologic reflexes, usually appearing during the terminal phase, and (5) death occurring from ten to fifteen years after the onset.

The histologic alterations were also characteristic and resembled those described in the more common, infantile form of the disease. Widespread alterations in cell structure were present throughout the brain. These consisted mainly of balloon-like swelling and deformation, with deposition of lipoids in the cytoplasm. Other cells might be shrunken or missing. The nucleus was pushed to the periphery or into

1. Sjögren, T.: Die juvenile amaurotische Idiotie: Klinische und erblichkeitsmedizinische Untersuchungen, *Hereditas* 14:197, 1931.

the base of the dendrites. The latter were frequently swollen or corkscrew. The structure of the nucleus was better preserved than that of the cytoplasm, though its wall might be hyperchromatic or even destroyed. Nissl substance was usually absent; it was rarely seen in the pyramidal cells of the cortex. In many of these cells the neurofibrils were completely replaced by lipoidal granules. In others a few neurofibrils might be seen adjacent to the cell wall.

Although some writers have expressed the opinion that granules consisting of neutral fat are characteristically seen in the juvenile form, in contrast to the prelipoids of the infantile form, this did not appear to be true in the present case, as the granules did not stain red with scarlet red.

Changes were present in all of the numerous cortical areas that were examined, in general decreasing in severity from the frontal to the occipital region. The pyramidal cells of the third and fifth layers showed the most striking alterations. Few of the cells retained their normal contour. A decrease in the number of cells was apparent, and numerous gaps were observed. No giant pyramidal cells were observed in the motor area. None of the other cortical laminae escaped involvement, however. The molecular layer appeared sclerotic; numerous swollen astrocytes were noted. The superficial tangential plexus was absent. A few degenerating horizontal cells of Cajal were seen in this layer. Ostertag² noted them in the infantile form. These cells, which ordinarily disappear completely after birth, have been said to be a sign of arrested development.³ Alterations of the small pyramidal cells in the second layer were more difficult to detect than those in the third or fifth layers but were nevertheless, definite. Some of these cells were swollen, but most had only a fragment of cytoplasm adjacent to the nucleus. Regardless of its amount, the cytoplasm was filled with granules of the same type as those seen in the larger pyramidal cells. Ostertag observed only shrunken cells in the second layer, in contrast to the swollen ones seen elsewhere. He therefore made the assumption that there were two different types of degeneration. The evidence in the present case indicates that the small, lipid-containing cells may represent either a stage preceding swelling or subsequent shrinkage, similar to that seen in axonal degeneration. Most of the star cells in the fourth layer were swollen and filled with lipid. Many of the spindle cells of the

2. Ostertag, R.: Entwicklungsstörungen des Gehirns und zur Histologie und Pathogenese besonders der degenerativen Markerkrankung bei amaurotischer Idiotie, *Arch. f. Psychiat.* **75**:355-391, 1925.

3. Gerstmann, J.: Beitrag zur Kenntnis der Entwicklungsstörungen in der Hirnrinde bei genuiner Epilepsie, Idiotie, juveniler Paralyse und Dementia praecox, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **21**:286-313, 1916.

sixth layer had lost their normal contour and become rounded. The radial fibers and the bands of Baillarger were present in all regions of the cortex, while the tangential fibers and the superradiate and inter-radiate networks had partially disappeared. Diminution of the number of cells was not present in the region of the cornu ammonis, although swelling and lipoidosis were particularly striking in the larger ones. Many cells in the subiculum were normal in size and shape. This picture is in contrast to Scherer's⁴ description of a decrease in cells in the dorsal foliage of the cornu ammonis and its transition into the fascia dentata, while the cells of Sommer's sector remained comparatively intact.

Similar widespread alterations in structure have been reported by other investigators in various areas of the cortex in cases of the juvenile form of amaurotic idiocy. Their observations usually differ only in the relative intensity of the process in the different areas and layers. Schob,⁵ for instance, was unable to recognize any normal cells in the cortex. Globus⁶ also described a universal distribution of the lipoidosis in the cortex in his case. He stated that the third and fifth layers were especially affected, but that portions of the fourth layer were seriously involved in the area striata. Status spongiosus was present where the cells had disappeared. Greenfield and Holmes⁷ encountered no distinction in the degree of cell change in various regions except that some cells in the hippocampus were more diffusely swollen than any others in the cortex. They observed that the diminution in number of cells affected all layers indiscriminately. Taft and Monroe's⁸ case of the juvenile type was characterized by severe degeneration in the calcarine area and relative intactness in the hippocampal region; all layers were affected. In Hassin's⁹ case of the late infantile type the third, fourth and fifth layers of the occipital lobe were practically destroyed and replaced by neuroglia. In our case the cytoarchitecture was especially well preserved in this region. Involvement of all the

4. Scherer, H. J.: Die Ammonshornveränderungen bei der familiären amaurotischen Idiotie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **138**:481-492, 1932.

5. Schob, F.: Zur pathologischen Anatomie der juvenilen Form der amaurotischen Idiotie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **10**:303-324, 1912.

6. Globus, J. H.: Ein Beitrag zur Histopathologie der amaurotischen Idiotie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **85**:424-466, 1923.

7. Greenfield, J. G., and Holmes, G.: The Histology of Juvenile Amaurotic Idiocy, *Brain* **48**:183-217, 1925.

8. Taft, A. E., and Monroe, J. P.: Familial Preadolescent Mental Deterioration and Blindness, *Am. J. Psychiat.* **5**:87-92, 1925.

9. Hassin, G. B.: A Case of Amaurotic Family Idiocy, Late Infantile Type (Bielschowsky) with Clinical Picture of Decerebrate Rigidity, *Arch. Neurol. & Psychiat.* **16**:708-727 (Dec.) 1926.

layers in all cortical areas was also described by Dide and van Bogaert,¹⁰ although they expressed the belief that the deeper layers were more severely damaged.

It may be concluded that cortical alterations consist mainly of (1) diffuse lipoidosis and swelling of ganglion cells; (2) completely asystematic, patchlike disappearance of cells, most striking in the third and fifth layers, and (3) sclerosis of the molecular layer with loss of tangential fibers.

It is remarkable that in spite of involvement of the vast majority of cortical cells the loss of function was not greater. While considerable mental deterioration had occurred, the patient nevertheless was cooperative and talkative; in tests of vocabulary and general comprehension he was at the 8 year level. As in most cases of the juvenile type of amaurotic idiocy, no sensory or auditory impairment was observed. No aphasia, agnosia or apraxia was present. Taft and Monroe⁸ stated: "The loss of vision is usually due to cortical degeneration, in contrast to the macular change and optic atrophy which is found in the infantile group." This appears to be unlikely in the present case. Not only was the calcarine area relatively less damaged than other portions of the cortex, but severe degenerative changes (retinitis pigmentosa with optic nerve atrophy) were present in the fundus.

The electroencephalographic activity was not particularly disorganized. In some areas no definite abnormalities were noted. Some random slow activity was present, particularly in the occipital region; none of this was of great amplitude. A fairly well organized electroencephalographic pattern was also noted in the case of Levy and Little¹¹; some 6 per second activity was observed in the frontal and central regions, but the alpha rhythm was well defined in the occipital region. When the electroencephalographic examination was repeated one year later, numerous delta waves of high amplitude had appeared. While in Levy and Little's¹¹ case the onset of grand mal convulsions was noted between the taking of the two records, in our case seizures had occurred prior to the recording of the relatively normal electroencephalogram. One is therefore unable to assert that any specific relation exists between the disorganization of electrical activity in the cortex and convulsions in this disease.

From these observations one is led to the conclusion that marked alterations in the cytoplasm of the ganglion cells with damage to neuro-

10. Dide, M., and van Bogaert, L.: *Sur l'Idiotie amaurotique juvénile* (type Spielmeier-Vogt), *Rev. neurol.* **69**:1-42, 1938.

11. Levy, S., and Little, O. A. G.: *Juvenile Familial Amaurotic Idiocy* (Vogt-Spielmeier Disease), *Arch. Neurol. & Psychiat.* **44**:1274-1289 (Dec.) 1940.

fibrils and loss of Nissl substance of the type noted in this case may not be of as great importance in the production of neurologic deficit and disorganization of the normal electroencephalographic pattern as is frequently supposed. The relatively moderate impairment of the cell nuclei and the almost complete intactness of the myelin sheaths and axons, in spite of the long course of the disease, is further indication of relative functional integrity, despite the striking alterations in cell structure.

The failure of most of the subarachnoid channels to fill in the air encephalogram and the elevated cerebrospinal fluid pressure may be correlated with the large size of the brain and the shallow sulci. This was apparently due to the swelling of the ganglion cells and the proliferation of glia.

SUMMARY

A case of the juvenile type of amaurotic family idiocy is described. An attempt is made to correlate the results of neurologic, psychologic, encephalographic and histologic studies, with particular reference to cortical activity. In spite of severe and widespread cellular alterations, many cortical functions were retained, and the electroencephalographic pattern was not especially impaired.

Stanford University Hospitals, San Francisco.

630 West One Hundred and Sixty-Eighth Street, New York.

SURGICAL HISTORY OF TRIGEMINAL NEURALGIA

ARNOLD M. MEIROWSKY, M.D.

AND

FEORI F. PIPITO, M.D.

ALBANY, N. Y.

It has been said that Hippocrates, Aretaeus, Galen and others referred to trigeminal neuralgia and that the condition was mentioned as early as 400 B. C. Bretschneider,¹ in his monograph on the external neuralgias, referred to the accounts of these ancient writers; none of them, however, was sufficiently accurate to justify the diagnosis of trigeminal neuralgia. Avicenna (980-1036 A. D.), of the Arabic school of medicine, is often cited as having described trigeminal neuralgia, but Lewy,² who was the first to translate correctly Avicenna's work, indicated that he dealt with facial paralysis and facial spasm rather than with a disorder affecting the fifth nerve.

According to Lewy, the first authentic case of tic douloureux was recorded by Bretschneider. He, on the other hand, failed to distinguish this case from numerous others in which the condition undoubtedly did not belong to the trigeminal neuralgias. According to Lewy, Johannes Laurentius Bausch, municipal counselor, physician and philosopher, founder and first president of the Imperial Leopoldinian Academy of Natural Sciences in Schweinfurt, Franconia (Bavaria), suffered for years from trigeminal neuralgia. He finally died in 1665 of complications occasioned by this, at that time, incurable disease. The eulogy written by the secretaries of the academy, Dr. Johannes Michael Fehr and Dr. Elias Schmidt, gives an account of Dr. Bausch's illness and death. The outstanding features of the disease as known today are described in this eulogy, which was published in 1672.

During the following year numerous similar cases were reported. Well known in the literature is the instance described by the author and philosopher John Locke.³ In one of his almanacs he recounted the story of the Countess of Northumberland, wife of the English ambassador to Paris, and gave a detailed account of the signs and symptoms of her

From the Department of Neurosurgery of the Albany Hospital and Medical College, Union University.

1. Bretschneider, H.: Versuch einer Begründung der Pathologie und Therapie der äusseren Neuralgien, Jena, F. Mauke, 1847.

2. Lewy, F. H.: The First Authentic Case of Major Trigeminal Neuralgia, Ann. M. Hist. 10:247, 1938.

3. Locke, J.: The Celebrated Locke as Physician, Lancet 2:367, 1828.

illness. This layman's description is accurate enough to permit the diagnosis of trigeminal neuralgia.

André,⁴ in 1756, first spoke of trigeminal neuralgia as "tic douloureux." In 1776 Sir John Fothergill⁵ gave the first classic description of this disorder. For a long time after this trigeminal neuralgia was referred to as "Fothergill's disease."

The surgical history of trigeminal neuralgia reveals a centripetal approach to the problem. With the passing of time the tendency has been to substitute central and more radical measures for the relatively ineffective peripheral approaches. This history is divisible into four periods—those of operations on the peripheral nerves, on the ganglion, on the sensory root and on the central connections in the brain stem respectively.

The first period in the operative history is concerned with procedures limited to the peripheral nerves. These include neurotomy, neurectomy, extraction of the nerve and nerve stretching.

Neurotomy, simple cutting of the nerve, was performed by Galen⁶ as early as 180 A. D. In spite of the ineffectiveness of this operation, it was still being employed as late as 1840. The branches of both the fifth and the seventh nerve were sectioned in the face. In those days these nerves were not differentiated physiologically, and as a result were considered equally responsible for the pain. In the words of Monro, a surgeon of the latter part of the eighteenth century, "two nerves were given to the face lest by accidental division of one the face should be deprived of nervous power altogether."

It remained for Sir Charles Bell,⁷ in 1820, to show the folly of this false belief with his clinical and experimental observations which differentiated the fifth and the seventh nerve. In spite of this work, Bell complained that many surgeons of that period continued to section the seventh nerve for the relief of tic douloureux. However, in time Bell's work became universally accepted, and the relation of the trigeminal nerve to tic douloureux was established.

Neurectomy was recommended by Abernethy⁸ in 1793 as a means of preventing recurrences of the neuralgia. Many modifications inevitably followed. Von Klein,⁹ in 1822, crushed and cauterized the

4. André, N.: *Observations sur les maladies de l'urèthre et sur plusieurs faits convulsifs*, Paris, Delaguette, 1756, p. 323.

5. Fothergill, J.: *Of a Painful Affection of the Face*, Med. Obs. Soc. Phys. 5:129, 1776.

6. Galen, cited by Horsley, Taylor and Colman.²¹

7. Bell, C.: *The Nervous System of the Human Body*, Washington, D. C., Duff Green, 1833.

8. Abernethy, J.: *Surgical and Pathological Essays*, London, J. Evans, 1793.

9. von Klein: *Ueber die Möglichkeit der Zerstörung des Gesichtsnerven bei seinem Austritt aus dem Schädel*, J. d. Chir. u. Augenh. 3:46-61, 1822.

central end. Malgaigne¹⁰ split the central portion longitudinally and looped it back. Other workers interposed soft tissues between the divided ends. These refinements, the products of cerebration and frustration, were indeed ingenious, but it appears that the time for successful treatment of tic douloureux had not yet arrived.

Evulsion of the peripheral nerve, merely an extension of neurectomy in which a greater portion of the nerve was removed, represented another unsuccessful attempt at therapy. Thiersch¹¹ developed this method to its fullest degree, attacking all three branches of the trigeminal nerve and removing the nerve almost in its entirety.

Stretching the nerve was first introduced by von Nussbaum¹² in 1872. Vogt,¹³ however, first employed it in 1876 for tic douloureux. Unfortunately, he too was unsuccessful.

The operations on the smaller peripheral branches later gave way to those centering about the three divisions of the nerve. Many methods were devised to reach each division. Warren,¹⁴ in 1828, was the first to section a nerve proximal to its foramen. He used the trephine to reach the inferior maxillary nerve. The names of Lücke,¹⁵ Braun,¹⁶ Lossen,¹⁷ Pancoast,¹⁸ Krönlein,¹⁹ Velpeau,²⁰ Horsley and associates,²¹ Carnochan²² and many others were associated with this operation.

10. Malgaigne, J. F.: *Manuel de médecine opératoire, fondée sur l'anatomie normale et l'anatomie pathologique*, ed. 4, Paris, Germer-Baillière, 1843, p. 53.

11. Thiersch, C.: Ueber Extraction von Nerven, mit Vorzeigung von Präparaten, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 18:44, 1889; cited by Rose.²⁴

12. von Nussbaum, J. N.: Blosslegung und Dehnung der Rückenmarksnerven; eine erfolgreiche Operation, *Deutsche Ztschr. f. Chir.* 1:450, 1872.

13. Vogt, P.: Die Nerven-Dehnung als Operation in der chirurgischen Praxis; eine experimentelle und klinische Studie, Leipzig, F. C. W. Vogel, 1877.

14. Warren, J.: *Cases of Neuralgia*, Boston M. & S. J. 1:1, 1828.

15. Lücke, A.: Ausschneidung des zweiten Astes des Nervus trigeminus nach temporärer Resektion des Jochbogens, *Deutsche Ztschr. f. Chir.* 4:322, 1875.

16. Braun, H.: Neurektomien des zweiten Astes des Nervus trigeminus nach osteoplastischer Resektion des Jochbeines, *Centralbl. f. Chir.* 9:249, 1882.

17. Lossen, H.: Neurektomie des zweiten Astes des Trigeminus nach osteoplastischer Resektion des Jochbeines, nebst Vorschlag zu einer neuen Schnittführung, *Centralbl. f. Chir.* 5:65, 1878.

18. Pancoast, J.: *New Operation for the Relief of Persistent Facial Neuralgia*, Philadelphia M. Times 2:285, 1871-1872.

19. Krönlein, R. U.: Ueber eine Methode der Resektion des zweiten und dritten Astes des N. trigeminus unmittelbar am Foramen rotundum und ovale, *Deutsche Ztschr. f. Chir.* 20:484, 1884.

20. Velpeau, cited by Obalinski, A.: Ueber die temporäre Resektion des Unterkiefers behufs Vornahme der Neurectomie des dritten Trigeminusastes, *Wien. med. Presse* 30:337-340, 1889.

In this first period the operative approach was based on the anatomic distribution of the trigeminal nerve. The results of many of these operations were both sad and ghastly: sad because the pain invariably recurred, and ghastly because the cosmetic result was rarely considered. The removal of bone and tissue was undertaken with few scruples by the surgeon in an attempt to reach the nerve.

The second period in the operative history is concerned with the gasserian ganglion. Carnochan, in 1858, first proposed removal of this ganglion. For nearly thirty years the operation remained unrecognized, until Abbé,²³ in 1889, employed Carnochan's approach in a case of tic douloureux. Two years later (1891) Horsley and associates²¹ devised an operation in which the gasserian ganglion was removed by a temporal approach, but in the 1 case in which it was attempted the patient died. Credit for the first successful removal of the gasserian ganglion and the peripheral nerves belongs to Rose,²⁴ who in 1892 approached the ganglion by trephining the base of the skull through the pterygoid region. The operative approach which enjoyed the most success was developed by Hartley,²⁵ also in the same year. He reached the ganglion through the temporal region immediately above the zygoma.

With the increased effectiveness of operative relief of pain, neurosurgeons turned their efforts toward a reduction in the complications and the mortality. Tiffany,²⁶ in 1896, suggested the refinement of partial ganglionectomy in an effort to reduce the postoperative trophic disturbances of the cornea. He based his proposal on 2 observations which he derived from a review of 108 operations on the ganglion, in which the methods of Rose,²⁴ Hartley,²⁵ Krause,²⁷ Horsley and associates²¹ and Doyen²⁸ were used. Tiffany stated:

The first division is never involved alone, involvement being due entirely to reflex irritation. . . . Complications ensue when the first branch is removed.

21. Horsley, V.; Taylor, J., and Colman, W. S.: The Various Surgical Procedures Devised for the Relief or Cure of Trigeminal Neuralgia, *Brit. M. J.* **2**:1139, 1191 and 1249, 1891.

22. Carnochan, J. M.: Exsection of the Trunk of the Second Branch of the Fifth Pair of Nerves, Beyond the Ganglion of Meckel, for Severe Neuralgia of the Face, with Three Cases, *Am. J. M. Sc.* **35**:134, 1858.

23. Abbé, R.: The Surgical Treatment of Inveterate Tic Douloureux, *New York M. J.* **50**:121, 1889.

24. Rose, W.: Abstracts of the Lettsomian Lectures on the Surgical Treatment of Trigeminal Neuralgia, *Lancet* **1**:71, 182 and 295, 1892.

25. Hartley, F.: Intracranial Neurectomy of the Second and Third Divisions of the Fifth Nerve, *New York M. J.* **55**:317, 1892.

26. Tiffany, L. M.: Intracranial Operations for the Cure of Facial Neuralgia, *Ann. Surg.* **24**:575, 1896.

27. Krause, F.: Entfernung des Ganglion Gasseri und des central davon gelegenen Trigeminstammes, *Deutsche med. Wchnschr.* **19**:341, 1893.

28. Doyen, E.: Extirpation of the Gasserian Ganglion, *Ann. Surg.* **23**:69, 1896.

Another proposal of Tiffany's was to modify the Hartley-Krause operation so as to preserve the motor root. Cushing,²⁹ in 1900, developed the "infra-arterial" approach to the ganglion in an effort to reduce further the operative mortality. In this operation the zygoma was resected and the trephine opening made beneath the arch of the middle meningeal artery.

The third period in the operative history was introduced by Frazier and Spiller,³⁰ but it actually goes back to Horsley's unsuccessful attempt in 1891 to remove the gasserian ganglion, with section of the sensory root. If Horsley's patient had lived the benefits of this operation might have been recognized earlier. The high mortality in ganglionectomies led Frazier and Spiller to seek an operation with less danger to the patient. The results of their experiments developed into the operation in which the sensory root is sectioned—"a physiological extirpation of the Gasserian ganglion." The first successful operation of this type was performed by Frazier in 1901, in which the sensory root was approached by the Hartley-Krause technic. Although the motor root was sectioned at this operation, Frazier maintained that it could be spared.

Spiller and Frazier,^{30a} Bregmen³¹ and van Gehuchten³² performed excellent histoanatomic studies of the trigeminal pathways. These investigators observed that a definite anatomic relation exists between the various components of the trigeminal nerve, not only in the peripheral divisions but in the ganglion, the sensory root and the spinal root. They noted that the ventral portion of the spinal root corresponds to the medial portion of the sensory root and the dorsal portion of the spinal root to the lateral portion of the sensory root. Thus, since the central and peripheral prolongations of the gasserian ganglion preserve a definite spatial arrangement, it was reasoned that the ganglion also must have a definite order of arrangement. Tiffany's suggestion of

29. Cushing, H.: A Method of Total Extirpation of the Gasserian Ganglion for Trigeminal Neuralgia by a Route Through the Temporal Fossa and Beneath the Middle Meningeal Artery, *J. A. M. A.* **34**:1035 (April 28) 1900.

30. (a) Spiller, W. G., and Frazier, C. H.: The Division of the Sensory Root of the Trigeminal for the Relief of Tic Douloureux, *Univ. Pennsylvania M. Bull.* **14**:341, 1901. Frazier, C. H., and Spiller, W. G.: Physiologic Extirpation of the Ganglion of Gasser: Further Report on Division of the Sensory Root for Tic Douloureux, Based on the Observations of Four Cases, *J. A. M. A.* **43**:943 (Oct. 1) 1904.

31. Bregmen, E., in Obersteiner, H.: *Arbeiten aus dem Institut für Anatomie und Physiologie des Centralnervensystems an der Wiener Universität*, Leipzig, F. Deuticke, 1892, pp. 88-92.

32. van Gehuchten, A.: The Surgical Treatment of Trifacial Neuralgia, *Univ. Pennsylvania M. Bull.* **17**:50, 1904.

sparing the inner third of the ganglion in order to preserve vision was thus substantiated.

It was felt that at last the ideal treatment for tic douloureux had been found. But some of the complications of the operation on the sensory root, such as trophic ulceration of the cornea and paralysis of the motor division of the trigeminal nerve, were still to be eliminated. Frazier,³³ in 1921, offered a refinement in which the motor root was spared. He suggested the use of an electrode not only to identify this root but to allay any fear that a sensory fasciculus was left behind. In 1925 he³⁴ employed subtotal resection of the sensory root, with section only of the outer two thirds. A still more precise refinement was instituted in 1928 by Stookey,³⁵ who advocated the differential section of the sensory root, depending on the area of the face involved.

Dandy,³⁶ in 1925, developed the suboccipital approach to the sensory root at the pons. With this pontile approach he succeeded in avoiding the complications commonly met with in the temporal approach.

The fourth period in the operative history is still in the formative stage. It is concerned with section of the tract in the brain stem. Anatomically, section of the tract is ideal because it eliminates only the pain fibers. Serra and Néri,³⁷ in 1936, sectioned the quintothalamic tract. Sjöqvist,³⁸ in 1938, sectioned the bulbospinal tract of the trigeminal nerve within the medulla oblongata. Unfortunately, serious complications from this operation have been reported. Olivecrona³⁹ has already suggested an improvement in the technic which supposedly eliminates the danger of laryngeal palsy and disturbance of gait and station. However, too short a period has elapsed for the proper evaluation of these procedures.

33. Frazier, C. H.: A Refinement in the Radical Operation for Trigeminal Neuralgia, *J. A. M. A.* **76**:107 (Jan. 8) 1921.

34. Frazier, C. H.: Subtotal Resection of Sensory Root for Relief of Major Trigeminal Neuralgia, *Arch. Neurol. & Psychiat.* **13**:378 (March) 1925.

35. Stookey, B.: Differential Section of Trigeminal Root in Surgical Treatment of Trigeminal Neuralgia, *Ann. Surg.* **87**:172, 1928.

36. Dandy, W. E.: Section of Sensory Root of Trigeminal Nerve at Pons, *Bull. Johns Hopkins Hosp.* **36**:105, 1926; An Operation for the Cure of Tic Douloureux, *Arch. Surg.* **18**:687 (Feb.) 1929.

37. Serra, A., and Néri, V.: Die elektro-chirurgische Unterbrechung der Zentralbahnen des V. Paares am lateralen ventralen Rand des Pons Varoli als erster Behandlungsversuch von hartnäckigen Neuralgien des Trigeminus durch Tumoren der Schädelbasis, *Zentralbl. f. Chir.* **63**:2248, 1936.

38. Sjöqvist, O.: Eine neue Operationsmethode bei Trigeminusneuralgie. Durchschneidung des Tractus spinalis trigemini, *Zentralbl. f. Neurochir.* **2**:274, 1938; Trigeminal Neuralgia: A Review of Its Surgical Treatment and Some Aspects of Its Etiology, *Acta chir. Scandinav.* **82**:201, 1939.

39. Olivecrona, H.: Tractotomy for Relief of Trigeminal Neuralgia, *Arch. Neurol. & Psychiat.* **47**:544 (April) 1942.

Although tic douloureux today is curable, little if anything is known of its cause. Many theories have been advanced; none so far has proved accurately to explain its cause.

The centripetal development of operative procedures for tic douloureux indicates a distinct advancement in surgical science. In the words of Oliver Wendell Holmes, "The great thing in this world is not so much where we stand, as in what direction we are moving."

Dr. E. H. Campbell and Dr. T. J. C. von Storch gave helpful criticism and suggestions.

Albany Medical College.

FOREIGN BODY GRANULOMAS PRODUCED BY SURGICAL COTTON

FRANK H. MAYFIELD, M.D.

AND

WILLIAM McKEE GERMAN, M.D.

CINCINNATI

A case of fatal adhesive or proliferative arachnoiditis resulting from particles of surgical cotton (cottonoid¹) left at operation prompted the study of which this paper is a report. Because of the observations in this case we have reexamined all of the material we had available in cases in which autopsy had followed operation or in which a previous operation had been done, and in nearly every instance we found that occasional cottonoid fibers had been left and that about them there was a foreign body reaction of a granulomatous type. In most of the specimens the amount of cottonoid was scant and the amount of tissue reaction so slight that it could hardly have been of clinical significance. Yet we feel that in many instances some fibers of cotton or cottonoid left in the wounds, depending on the amount and location, are capable of producing a reaction that will obstruct circulation of the cerebrospinal fluid.

It has been known for many years that cotton buried in tissues produces granulomas (Spies, Mandeville and Awdziejewicz²). Nevertheless, though pledgets of cotton or the proprietary preparation cottonoid have been widely used as absorbent sponge material during neurosurgical operations, we have found no reference to this subject. The lack of previous clinical reports may be explained by the fact that since the cellulose fibers are relatively inert chemically, they do not stain by any of the ordinary methods and are, therefore, not readily visualized by

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From the Departments of Neurosurgery and Pathology, Good Samaritan Hospital.

1. Cottonoid is described by Johnson & Johnson as "a compressed lightly-embossed and lightly-sized cotton sheet. It is prepared from a web of our best grade surgical cotton (i. e., comparable to Red Cross cotton), which stock is passed under an embossing roll with a light sizing solution, the pressure and size contributing toward bonding and strengthening of the sheet. This size bath consists of approximately 2% dextrinized corn starch and 0.8% boric acid."

2. Spies, J. W.; Mandeville, F. D., and Awdziejewicz, F. J.: Nature and Result of Animal Tissue Reactions to Cellulose, *Proc. Soc. Exper. Biol. & Med.* **30**:420-425, 1933.

the transmitted light of the standard microscope. When sections containing cottonoid are studied under polarized light, the fibers of cellulose stand out brightly in the darkened field.

The case of adhesive arachnoiditis referred to in the opening paragraph justifies a brief report.

REPORT OF A CASE

Sister M. D., a white woman aged 23, was admitted to the Good Samaritan Hospital in Cincinnati on Nov. 15, 1939 with the complaint of recurring bouts of vertigo and slight tinnitus in the left ear. She had not experienced headache. The fundi were normal. There was hypesthesia of the left cornea. During the bouts of vertigo, nystagmus was present, and there was pronounced unsteadiness of gait, with a tendency to fall to the left. Between the bouts there was no ataxia and no alteration of gait and station.

On November 18 a lumbar puncture was done. The initial pressure, with the patient in the horizontal position, was 140 mm. of water. The fluid was clear and colorless. The cell count was 0; the protein content was 30 mg. per hundred cubic centimeters, and the Wassermann reaction was negative.

Roentgen examination of the skull revealed no pathologic change.

Prior to admission, intensive medical therapy (potassium chloride and histamine phosphate) had been given for several months, without benefit. It was suspected that the patient had a tumor in the left cerebellopontile angle, and it was decided to explore this area, with the plan of dividing the vestibular portion of the eighth nerve if no tumor was encountered.

On November 27, with the use of procaine anesthesia, the left cerebellar fossa was explored. No tumor was seen. The vestibular portion of the eighth nerve was divided. During the course of the operation a pledget of cottonoid, identified with a silk suture, was placed between the tonsils of the cerebellum to prevent oozing blood from entering the fourth ventricle. On the fourth postoperative day, the patient had begun to complain of severe headache and showed evidence of increased intracranial pressure. A lumbar puncture released blood-tinged fluid under 350 mm. of pressure.

Because a hematoma was suspected, the wound was reopened on Dec. 1, 1939. There was about 1 teaspoon of clotted blood in the extradural space. The tonsils of the cerebellum were adherent to each other. They were released. Immediately after operation the patient appeared in good condition, but three days later there was again evidence of increased intracranial pressure. Attempts to control this pressure by repeated ventricular and spinal taps were unsuccessful.

On Jan. 5, 1940 ventriculographic examination and exploration of the posterior fossa were carried out. The arachnoid and pia about the lower pole of the cerebellum were greatly thickened, and the cerebellar tonsils were densely adherent to each other, so that the foramen of Magendie was occluded. Insofar as possible, the normal pathways of the cerebrospinal fluid were reestablished by separation of the adherent surfaces, and for about ten days the intracranial pressure seemed to be controlled. Thereafter, the area of decompression again began to bulge, and it was obvious that the circulation of the cerebrospinal fluid was again obstructed.

On January 19 a third ventriculostomy was done; except for moderate hyperthermia, the patient did fairly well until the end of the third day, when she had a sudden convulsive seizure. Thereafter, she remained in coma until her death, six hours later.

Autopsy was performed three hours after death. There was nothing remarkable about the cerebral hemispheres, except for marked dilatation of the entire ventricular system and the surgical opening in the wall of the third ventricle. About the brain stem, however, the leptomeninges were greatly thickened, and this reaction spread over the inferior surface of the cerebellum. The cerebellar tonsils were densely adherent to each other, and the foramen of Magendie was occluded. In the upper portion of the fourth ventricle there was a small tumor nodule, measuring 7 mm. in diameter. This tumor, on microscopic examination, proved to be an ependymoma of low grade malignancy. We were convinced that it was not of sufficient size to have occluded the fourth ventricle.

Microscopic examination of the thickened leptomeninges showed an extensive productive reaction characterized by the formation of granulomas, which in certain areas bore a striking resemblance to tubercles. Associated with the granulomas were diffuse proliferation of fibroblasts, much edema and a collection of lymphocytes and giant cells. Under polarized light, there were seen numerous fragments of cottonoid material, each fragment serving as a nucleus for the formation of a granuloma. There was no evidence of pyogenic infection (fig. 1).

OTHER MATERIAL

In all, 12 specimens from operative cases were reexamined. In 8 of the 12 cases we were able to find an occasional fiber of cottonoid, and in each instance a granuloma surrounded the fiber.

In figure 2 are shown sections of a granuloma observed at autopsy in the bed from which an acoustic neurinoma had been removed. The patient had bilateral acoustic neurinoma and a meningioma in the posterior fossa. Death followed the attempt to remove an acoustic neurinoma on the right side.

COMMENT

This group of cases had one thing in common, the production of foreign body granulomas. These granulomas were characterized by a tissue reaction consisting of the proliferation of fibroblasts, with some of the cells resembling epithelioid cells; the accumulation of certain wandering cells, most of which were monocytes and lymphocytes, and the appearance of multinucleated giant cells about foreign body elements, which in this instance were cellulose fibers. In certain cases the granulomas resembled tubercles, and in 1 instance the resemblance was so striking that special stains were carried out to eliminate the presence of tuberculosis.

For the most part, the granulomas occur, as might be supposed, in the arachnoid and cause extensive chronic productive arachnoiditis, which, depending on the degree and location, may lead to obstructive phenomena. When the cellulose material is scanty, its recognition may be difficult. Of great aid in its identification is the use of polarized light.

It was interesting to note in the specimens examined that when the field of operation was small, so that pledgets of cottonoid were repeatedly

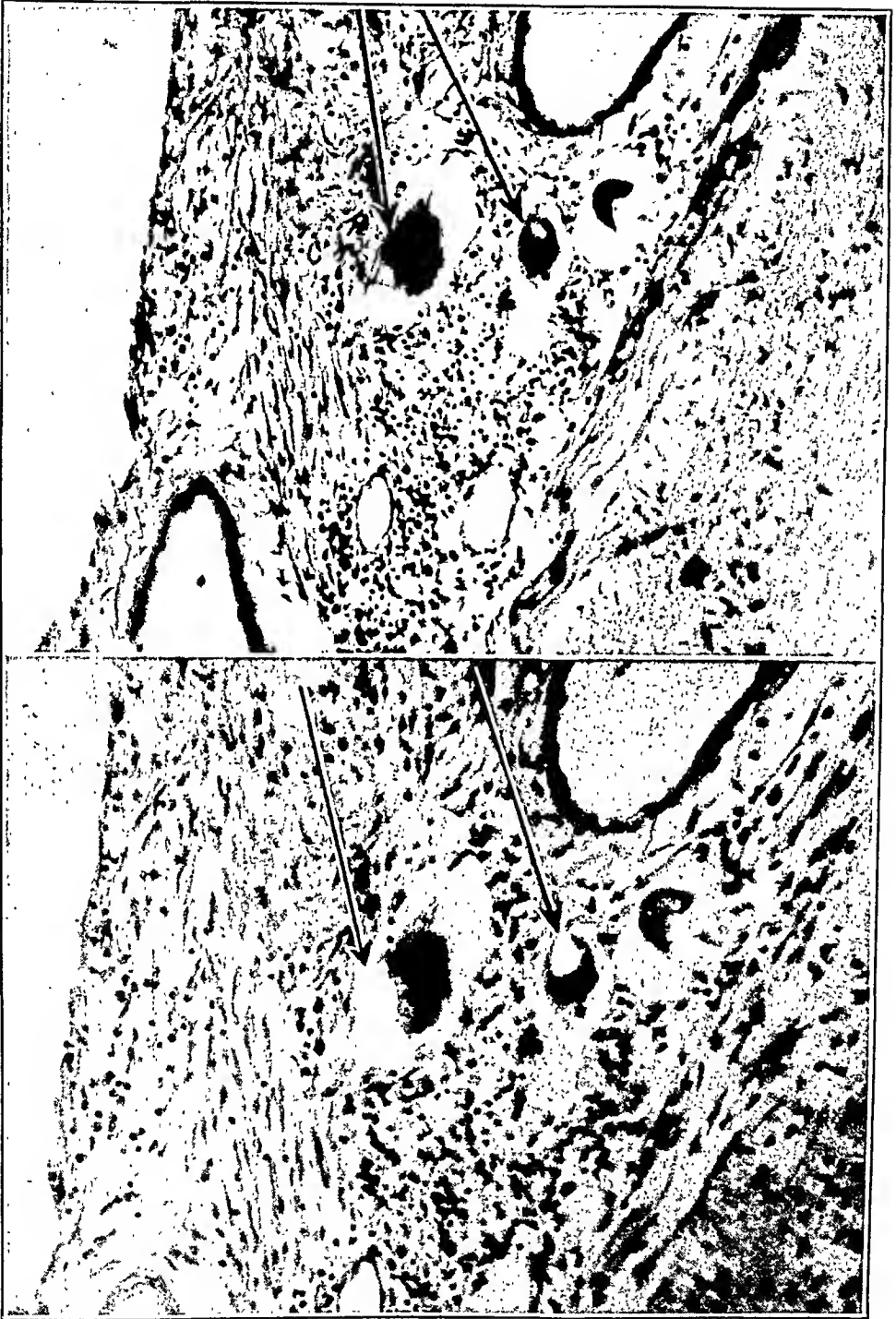


Fig. 1.—Tuberculous-like reaction in the human basilar meninges produced by cottonoid used as a surgical sponge. With ordinary illumination (above) the cottonoid fibers which are being attacked by giant cells in the arachnoid, escape attention, while with polarized light (below) the material becomes obvious.

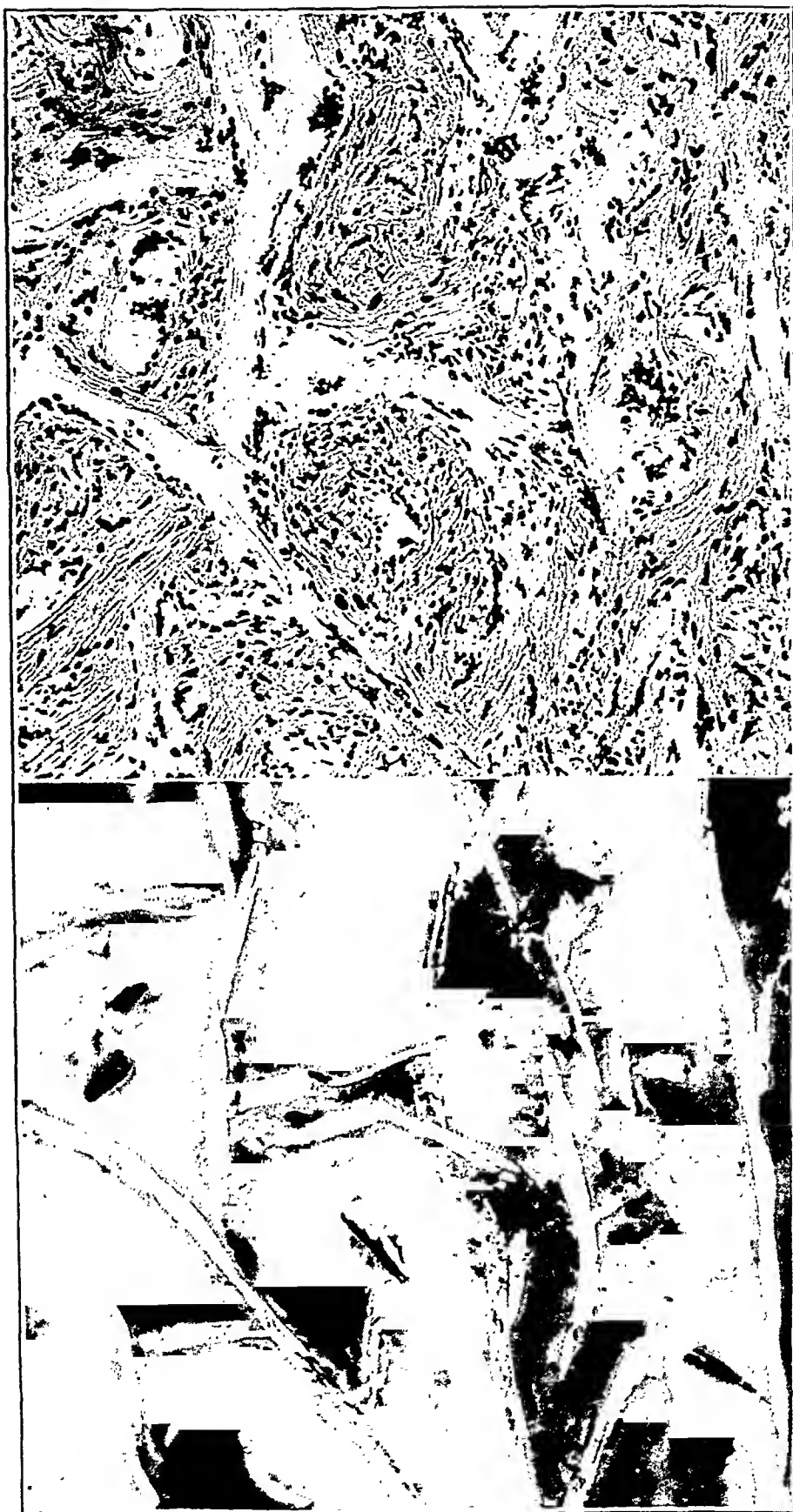


Fig. 2.—Above, photomicrograph of a thickened arachnoid viewed with ordinary illumination and slightly out of focus. The cottonoid fibrils are barely perceptible.

Below, the same microscopic field viewed with polarized light. The same fibrils stand out dramatically in illumination against a darkened field.

Hortega silver impregnation.

pushed in and out of small openings, the amount of material left was greater. When the field of exposure was large, the amount left was minimal.

It is not our intention to condemn the use of cotton or cottonoid. However, it does seem well, in view of the general use of these materials, to call attention to the possibility of fibers being detached and left in the field of operation. Thorough irrigation of the wound would probably remove all particles. Cottonoid has been used exclusively by us as absorbent sponge material in preference to standard cotton. We do not feel that the reaction described is the result of any inherent chemical property of this proprietary product, but rather that it would occur as a response to any nonabsorbable foreign body left in the tissues.

SUMMARY

A case of fatal adhesive arachnoiditis resulting from foreign body reaction to surgical cotton is reported. Observations in other cases in which fibers of this material were left at operation are commented on.

COMPARISON OF METRAZOL CONVULSIVE THERAPY WITH ELECTRIC SHOCK IN TREATMENT OF SCHIZOPHRENIA

EVALUATION OF RESULTS OBTAINED IN TREATMENT OF
ONE HUNDRED SCHIZOPHRENIC PATIENTS
WITH ELECTRIC SHOCK

LEON REZNIKOFF, M.D.

Clinical Director, Hudson County Hospital for Mental Diseases
SECAUCUS, N. J.

In 1940 I reported¹ results obtained in the treatment of 100 schizophrenic patients with metrazol convulsive therapy. A similar study has been conducted during the past one and one-half years in the treatment of 100 schizophrenic patients with electric shock. The present group was composed approximately of the same type of psychiatric material as that employed in the first study.

It has been emphasized by several writers that the difference in diagnostic criteria used by various clinicians in arriving at the diagnosis of schizophrenia is responsible for contradictory reports as to the results obtained with shock therapy in many hospitals. It is even debatable at present whether the term schizophrenia is actually limited to one mental disorder or may include a variety of similar psychiatric conditions. Besides, patients seen by psychiatrists in private practice and outpatient mental hygiene clinics are often of different type than those committed to public institutions. In psychiatric clinics one is apt to see more patients with borderline disorders without deterioration. In private hospitals patients are encountered of higher social, economic and educational level. Hence, tremendous discrepancies are noticed in the reports on results obtained with shock therapy by various workers in all sorts of institutions.

MATERIAL

The present study was made on patients admitted to the same public hospital, which derives patients from a comparatively small community of approximately the same social level as that represented two years ago when the results with metrazol-treated patients were reported. The two groups were essentially the same, and special effort was made to compare each group as to type of schizo-

1. Reznikoff, L.: Evaluation of Metrazol Shock in Treatment of Schizophrenia: Report of Results in One Hundred Cases, Arch. Neurol. & Psychiat. 43:318-325 (Feb.) 1940.

phrenia, duration of psychosis, mode of onset and precipitating factors, duration of hospitalization prior to treatment, age, sex, factors of chronicity, tendency to deterioration and hospital atmosphere, including psychologic influences during the administration of shock therapy.

Each group included only patients whose condition could be diagnosed as schizophrenia without the slightest doubt. All patients in each group were presented at the staff conference before administration of shock therapy, so that only patients whose psychosis was definitely diagnosed as schizophrenia were used in this study. At the completion of treatment, they were again presented at the staff conference and classified as "with remission," "much improved," "improved" and "not improved" (these terms having been in a previous communication¹).

PROCEDURE

Since the technic of administration of electric shock therapy has been adequately described in many papers and is comparatively simple, it seems unnecessary to repeat it here. The electric shock machine manufactured by Rham, Inc., was used in this work. Treatment was given three times a week.

Of the 100 patients, 42 were men and 58 women. A total of 1,921 treatments was given, of which 1,160 resulted in generalized convulsive seizures. All degrees of reactions could be observed during the application of electric shock. At times, with a low voltage for a given patient, only slight flushing of the face or pallor and blinking of the eyelids were obtained. At other times typical petit mal attacks or intermediate reactions between petit and grand mal, or even abortive attacks of grand mal might result. However, it seems that generalized convulsive seizures that look like attacks of grand mal epilepsy must be produced in order to achieve therapeutic effect. A few patients treated with only petit mal attacks, because of mild contraindications, improved only slightly, and a drastic difference was noted when the type of convulsions induced was changed from petit to grand mal. In some exceptional cases, in which extreme caution was required because of an obvious physical contraindication, a course of petit mal attacks might be attempted. Ordinarily, if a grand mal seizure was not produced, another treatment was given in five to ten minutes; no harm was observed when this interval was shortened to two minutes. In fact, in 2 or 3 shock-resistant patients, when a grand mal seizure could not be induced with the highest voltage available with this machine, another treatment was given at once, with production of the desired generalized convulsion. Several other measures may be taken to produce a generalized seizure in patients who require higher voltage. For example, the interval between treatments may be lengthened from three times to twice a week, and in some exceptional cases even to once a week. An attempt was made to reduce the convulsive threshold by alkalinizing the patients with large doses of sodium bicarbonate. This procedure, however, was unsuccessful. In general, it may be stated that one rarely encounters this difficulty, that it does seem to occur more often in women than in men (perhaps because of thicker growth of hair over the area where the electrodes are applied) and that it is present in some older patients.

Since only schizophrenic patients were included in this group, the oldest was 53 and the youngest 15 years of age. As with metrazol treatment, the majority of patients gained weight, and only a few lost. However, the gain in weight with electric shock was considerably lower than that with metrazol. The average gain in weight with electric shock amounted to 6.4 pounds (2.9 Kg.) and that with

metrazol to 9.14 pounds (4.2 Kg.). It has also been noticed that the patients who failed to gain weight reacted poorly to the treatment and did not improve. Patients were allowed to have 8 to 12 generalized convulsive seizures; a few had 15; the average was 11.6 generalized convulsive attacks. A few patients relapsed two or three weeks after therapy was completed and then were given a few additional treatments, while 9 patients received a complete additional course after six to twelve weeks. In the metrazol-treated group, at first as many as 40 convulsive seizures of grand mal type were produced, and only later was it considered that if there was no improvement with 20 or 25 grand mal seizures further administration of metrazol therapy was useless, since in some patients satisfactory results were obtained with 10 seizures. Because the electric shock era followed the use of metrazol, some knowledge had been gained from electroencephalographic studies which indicated that rather persistent abnormal waves may follow prolonged convulsive therapy.² It seems best now not to allow a patient to have more than 12, or at the most 15, generalized convulsive attacks in one course of treatment. This caution is especially warranted since up to the present sufficiently comprehensive microscopic studies of human brain tissue after electric shock have not been made, obviously owing to lack of material.³

The longest duration of psychosis among the patients in this group was about ten years and the shortest six weeks. The average duration of illness was twenty-four and four-tenths months. According to the duration of psychosis, the patients were divided into four groups:

Duration	No. of Patients
Under 6 months	29
6 months to 2 years	40
2 years to 5 years	18
Over 5 years	13

They were classified as to the type of schizophrenia as follows:

Type	No. of Patients
Catatonic	20
Paranoid	63
Hebephrenic	14
Simple	3

RESULTS

Since relapses following any kind of shock therapy for schizophrenia are rather frequent, it is important to keep in mind that statistical results obtained immediately after treatment will differ considerably from those compiled after several months of observation of the patient.

In this group of patients, if remission was not maintained and the patient relapsed in a few weeks, he was classified as unimproved. The

2. Davis, P. A., and Sulzbach, W.: Changes in the Electroencephalogram During Metrazol Therapy, *Arch. Neurol. & Psychiat.* **43**:341-353 (Feb.) 1940. Pacella, B. L., and Barrera, S. E.: Some Considerations of the Electroencephalogram in the "Convulsive State," *J. Nerv. & Ment. Dis.* **96**:125-129 (Aug.) 1942.

3. Alpers, B. J., and Hughes, J.: Changes in the Brain After Electrically Induced Convulsions in Cats, *Arch. Neurol. & Psychiat.* **47**:385-398 (March) 1942.

present report was prepared two to eighteen months after completion of the treatment; that is, the first patient completed treatment with electric shock eighteen months ago and the last patient only two months ago. Table 1 shows the results of treatment according to the duration of schizophrenia, including the relapses.

As is seen in table 1, 68 patients were unimproved and 32 patients were improved (of these, 13 patients were classified as having achieved remission, 4 patients were much improved and 15 patients were improved). In the metrazol-treated group after relapses were taken into consideration, approximately the same results were obtained. In both groups better results were obtained in patients with a shorter duration of mental illness. Of the 29 patients treated with electric shock who were ill less than six months, 14 improved and 15 failed to improve, while in the group of 31 patients with duration of psychosis of more

TABLE 1.—*Results of Treatment According to Duration of Schizophrenia, Including Relapses*

Duration of Psychosis	No. of Patients	Patients with Remissions		Patients Much Improved		Patients Improved		Patients Not Improved	
		No.	Percent-age	No.	Percent-age	No.	Percent-age	No.	Percent-age
Under 6 mo.....	29	8	27.0	1	3.5	5	17.2	15	51.7
From 6 mo. to 2 yr.....	40	4	10.0	2	5.0	8	20.0	26	65.0
From 2 to 5 yr.....	18	0	0.0	1	5.55	1	5.55	16	88.9
Over 5 yr.....	13	1	7.7	0	0.0	1	7.7	11	84.6
Total.....	100	13		4		15		68	

than two years only 4 improved. It is difficult to say why some schizophrenic patients, even with a psychosis of relatively short duration, do not show any improvement, or very slight symptomatic change, while others achieve apparent remission, even though temporary. As with the metrazol method, one is frequently impressed with the rather sudden change in behavior of mute, negativistic, catatonic patients. But while they become better institutional patients and are easier to manage and their pronounced catatonia disappears, they frequently remain apathetic or relapse after a short time into an indifferent, emotionally shallow state and otherwise show the familiar schizophrenic pattern.

Table 2 gives detailed information as to the results obtained with each type of schizophrenia. It is interesting to note that of 20 catatonic patients, 9 improved and 11 failed to improve. Of 3 patients suffering from a simple type of schizophrenia, none improved. Only 2 schizophrenic patients who had been ill longer than five years improved, but when their case histories are studied, one finds that they had had several spontaneous remissions in the past and did not require continuous institutionalization. The impression is gained that convulsive shock

therapy shortens the duration of hospitalization and brings about improvement in patients who are inherently capable of spontaneous improvement.

COMPLICATIONS

The same contraindications and precautions considered for metrazol-induced convulsions are applicable in the use of electric shock. All patients prior to treatment had careful physical and neurologic examinations, and a roentgenogram of the chest, an electrocardiogram and serologic tests were made. On completion of treatment, they were submitted to another electrocardiographic test. The blood pressure was taken before treatment, immediately after the seizure and thirty minutes after treatment was given. At the end of the convulsive attack there were observed a considerable rise in the systolic blood pressure and a

TABLE 2.—*Results of Treatment According to the Type and the Duration of Schizophrenia, Including Relapses*

	Catatonic				Paranoid				Hebe- phrenic				Simple			
	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.
Patients with remissions.....	4	1	0	0	3	3	0	1	1	0	0	0	0	0	0	0
Patients much improved.....	0	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Patients improved.....	0	1	0	0	2	6	1	0	3	1	0	1	0	0	0	0
Patients not improved.....	4	7	0	2	10	16	11	7	1	2	3	2	0	2	1	0

drop in the diastolic pressure, but in a half-hour the blood pressure returned to the original level. During the treatment a small sandbag was placed between the shoulders, and the extremities were held downward. A tongue depressor well padded with gauze was kept between the teeth during the treatment. There were several dislocations of the lower jaw, which, however, did not present any difficulty; at the end of the convulsive seizure the jaw either dropped in place by itself, or the dislocation was easily reduced by the physician. One male patient had a fracture of the right hip, and another suffered an impacted fracture of the neck of the left humerus. Electrically induced convulsions seem milder than metrazol convulsions and, according to the claims of some workers,⁴ are less apt to cause fractures. There were no deaths in this series.

4. Smith, L. H.; Hughes, J.; Hastings, D. W., and Alpers, B. J.: Electroshock Treatment in the Psychoses, *Am. J. Psychiat.* **98**:558-561 (Jan.) 1942. Worthing, H. J., and Kalinowsky, L. B.: The Question of Vertebral Fractures in Convulsive Therapy and in Epilepsy, *ibid.* **98**:533-537 (Jan.) 1942.

Prolonged apnea occurred more often with electric shock than with metrazol; at times it was alarming, but in all my patients consciousness returned without application of artificial respiration. Cyanosis appeared deeper with electric shock than with metrazol therapy.

Vomiting was met with in an occasional patient, usually only after the first or second treatment, and was much rarer than with metrazol.

Psychomotor hyperactivity following treatment occurred only in exceptional cases and was much milder and lasted a shorter time than after metrazol. The restlessness, extreme fright and at times regression observed during metrazol treatment, especially after incomplete reactions, were practically eliminated with electric shock.

Amnesia for treatment and relative lack of anxiety and fear are perhaps the greatest advantages of electric shock over metrazol therapy. At times, however, in some patients apprehension was noticed, which was more marked for the first few treatments and gradually disappeared as the patient learned not to fear the treatment. A few patients, however, remained fearful throughout the treatment, although the fear was not as extreme as was commonly observed with metrazol.

The onset of the convulsive seizure was almost instantaneous after application of the electric shock, although in some patients the latent period was observed to last from a few seconds to ninety seconds, but this was rare. It was definitely shorter than with metrazol. Latent convulsive attacks were not observed with electric shock.

Neubuerger, Whitehead, Rutledge and Ebaugh,⁵ in a study of pathologic changes in the brains of dogs given repeated electric shocks, stated:

Some degree of neuropathologic change is to be expected in animals given electric shock of the same strength and duration as those observed clinically. Our results suggest that the histologic changes induced by electric shock in the brains of dogs are somewhat less severe than the changes we found following metrazol.

SUMMARY AND CONCLUSIONS

Approximately the same results were obtained in 100 schizophrenic patients treated with electric shock as in a similar group of patients treated with metrazol. Two to eighteen months after treatment was completed, 32 patients were improved and 68 were unimproved.

There is a pronounced tendency to relapse in schizophrenic patients treated with convulsive shock therapy.

While amelioration of psychotic symptoms and behavior occurs in many patients, the essential schizophrenic pattern remains unchanged.

5. Neubuerger, K. T.; Whitehead, R. W.; Rutledge, E. K., and Ebaugh, F. G.: Pathologic Changes in the Brains of Dogs Given Repeated Electrical Shocks, *Am. J. M. Sc.* **204**:381-387 (Sept.) 1942.

Convulsive shock therapy helps to achieve remissions earlier than routine institutional treatment and therefore diminishes the duration of hospitalization.

Electric shock therapy is preferable to metrazol therapy, as has been pointed out by many workers, because there are amnesia for the treatment, less fear and anxiety, painless shock and avoidance of repeated intravenous injections in resistive patients.

Its greatest value consists in aiding in the preparation of uncooperative patients for other therapeutic measures, such as psychotherapy, occupational and recreational therapy and general psychiatric management.

Hudson County Hospital for Mental Diseases.

NEUROPSYCHIATRIC SEQUELAE OF PARTIAL EXSANGUINATION

J. P. MURPHY, M.D.

WASHINGTON, D. C.

Experimental observations on animals in which complete or temporary arrest of the cerebral circulation has been effected indicate that profound clinical and pathologic sequelae are consequent on the procedure. Gildea and Cobb¹ discovered that periods of total anemia of no longer than ten minutes resulted in severe, permanent lesions of a necrobiotic character in the cerebral cortex of the cat. Using the dog as subject, Kabat and Dennis² produced unconsciousness, cessation of respiration and total abolition of reflexes by obstruction of the cephalic blood flow for fifteen to twenty minutes. The chronic picture was one of virtual decerebration.

The exact human counterpart of these controlled investigations is necessarily difficult to find. Several cases have been reported, however, in which sudden, and presumably complete, cerebral anemia was followed by the development of neuropsychiatric syndromes. Postmortem examination revealed the expected irreparable and extensive damage to the brain. The factors productive of ischemia in these cases were loss of blood and fall of intravascular pressure, singly or together. Wolf and Siris,³ under the heading "acute non-traumatic encephalomalacia," described the rapid advent of unconsciousness and the protean signs of neurologic deficit in 4 elderly patients who were operated on for neurosurgical conditions in the upright position. A precipitous and extreme drop in blood pressure occurred during the course of the procedure. Necropsy disclosed bilateral, hemorrhagic infarction involving the cortex and superficial subcortex of the brain, particularly in the parietal regions. None of the cerebral arteries was occluded. The case of another patient in whom evidences of widespread injury to the central nervous system appeared shortly after severe and protracted shock supervened during

From Saint Elizabeths Hospital.

1. Gildea, E. F., and Cobb, S.: *The Effects of Anemia on the Cerebral Cortex of the Cat*, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

2. Kabat, H., and Dennis, C.: *Decerebration in the Dog by Complete Temporary Anemia of the Brain*, Proc. Soc. Exper. Biol. & Med. **38**:864, 1938.

3. Wolf, A., and Siris, J.: *Acute Non-Traumatic Encephalomalacia Complicating Neurosurgical Operations in the Sitting Position*, Bull. Neurol. Inst. New York **6**:42, 1937.

operation was reported by Schnedorf, Lorhan and Orr.⁴ Exploratory laparotomy was conducted with the patient under spinal anesthesia. Coma, convulsive seizures, signs of disease of the pyramidal tract and irrational activity featured the postoperative course, and death occurred on the twenty-first day. The cortical gray matter was observed to be the seat of alterations in the ganglion cells and of devastation necrosis. Symmetric cerebral softening was observed by Foix, Chavany and Bascourret⁵ after ictus caused by massive venesection in elderly, arteriosclerotic persons.

These clinical contributions all treat of the relatively acute, fatal consequences of rapidly developing cerebral anemia. An unusual opportunity to study the long term effects of such a disaster was afforded by the case which follows. A middle-aged man, in previous good health, attempted suicide while in an involutional depression. Exsanguination almost resulted in death. Appropriate emergency measures saved his life, but he was left with severe neuropsychiatric disability, which is the subject of consideration.

REPORT OF A CASE

W. L., a 42 year old married white man, a lieutenant in the United States Naval Reserve, was admitted to Saint Elizabeths Hospital on April 14, 1942.

The family history was negative for neuropathic determinants. A short, mild depression followed the death of the patient's first wife. He subsequently remarried, and happily so. He is said to have been in excellent health all of his life.

In January 1942, he was assigned to a ship undergoing commission. Nothing save a tendency to overconscientiousness was remarkable about his conduct. On February 17 he was found unconscious, virtually pulseless and gasping for breath, bleeding from a deep incision in the left side of the neck which transected the external jugular vein and from a similar wound in the left wrist. These lacerations had been self inflicted with a razor blade.

By the time he was discovered the systolic blood pressure was low and the diastolic pressure could not be obtained. He was rushed to a hospital where the incisions were sutured and intravenous transfusions of blood and fluids given. On the third hospital day he was conscious and moderately cooperative but was completely aphasic, confused and disoriented. He was unable to find his way about the ward, dressed and undressed at inappropriate times and made irrelevant remarks.

He was transferred to the United States Naval Hospital, Jacksonville, Fla., on March 6. On admission to that institution neurologic examination revealed pallor of the optic disks, hoarseness of speech, possible diplopia and weakness of the left hand grip. He could not carry out complex commands. Nearly complete motor aphasia existed, and writing was scrawled and repetitious. He was disoriented and affectively obtunded. The total protein content of the spinal fluid was increased,

4. Schnedorf, J. G.; Lorhan, P. H., and Orr, T. G.: The Problem of Anoxia in Surgery and Anesthesia, *Arch. Surg.* **43**:169 (Aug.) 1941.

5. Foix, C.; Chavany, J. A., and Bascourret: Foyers de ramollissement simultanés dans les deux hémisphères, *Rev. neurol.* **32**:77, 1925.

and there was a midzonal colloidal gold curve, but the Kahn reactions of the fluid and the blood were negative. He refused to eat at first but later became ravenous. He remained confused and unaware of time or place, but the mood changed to one of quiet cheerfulness. He was removed to the United States Naval Hospital, Washington, D. C., and from there to Saint Elizabeths Hospital.

At the time of entrance to the last hospital the patient was rather happy, friendly and moderately cooperative but appeared dazed. There was no abnormality of mental content. Perception and comprehension were faulty. He was totally disoriented for time and stated that he was in "Tampa—no, no—Washington!" Memory for remote and recent events was impaired, as were retention and recall. He admitted the suicidal attempt, declared that he had been deeply depressed at the time and insisted that such a thing would never happen again.

Formal examination of the receptive, gnostic and expressive capabilities was rendered difficult by the patient's mental confusion and defects in memory. A prominent semantic component was evident in imperfect understanding and responses. The latter were fluctuating in their correctness. Speech was occasionally paraphrastic and jumbled. At times he was unable to name common objects correctly, misidentified words on a printed list and could not select articles of the same color. When the examiner whistled such familiar tunes as "Yankee Doodle," he carried on, but could not say which air he was humming. When he was asked to touch his nose with his right hand, he placed his left hand on the top of his head, recognized the failure and said, "I know what I want to do, but I can't do it." He could mimic movements only in a mirror fashion. Complicated commands, involving a temporal component, were consistently misunderstood and misapplied. He read accurately but without comprehension. He wrote his name correctly but put down his home address instead of the requested date. In letters he was forced to fall back on terms of endearment to fill in gaps in thought transmission.

He was unable to perform simple arithmetical calculation. Writing, as noted, often consisted of ejaculations or expletives and was irrelevant. There was decomposition of words. He confused right and left more often than he recognized them, and he misidentified fingers fairly consistently.

Examination of the cranial nerves revealed pallor of the optic disks, weakness of the left lateral rectus muscle with diplopia and hoarseness. The last condition was said to have existed only since the suicidal attempt. Greater power in the left arm than in the right was probably due to the patient's predominant left handedness. The fourth and fifth fingers of the left hand were weak and held in partial flexion. Pinprick was poorly appreciated in the corresponding sensory distribution of the ulnar nerve. He could not perform skilled movements with the left hand. The deep reflexes were accentuated in the legs and in the right arm. The cutaneous reflexes were intact, and there were no abnormal reflex signs.

There was almost complete atropognosia in the hands and feet. Astereognosis and decrease in position sense were present in the left hand. Vibratory sensation was diminished in the left leg to the iliac crest.

The lacerations were well healed. There was no evidence of generalized arteriosclerosis, and the blood pressure was 132 systolic and 80 diastolic. The results of a complete blood count, urinalysis and the Kahn test of the blood were all within normal limits. Indirect inspection of the larynx revealed paresis of the left vocal cord.

A psychometric study was attempted, the report of which follows: "He is so confused that he cannot understand the questions . . . It is useless to evaluate the mental level. He appears to have suffered great cerebral damage" (Dr. Winifred Richmond). The report of the Rorschach test (Dr. Isabelle Kendig) was as

follows: "Severe, organic disease of the brain is indicated. . . . Little can be said of the patient's original makeup, although certain signs which point to an anxious, cautious, meticulous approach to life lend support to the diagnosis of involutional melancholia made at the Navy Hospital."

Repeated electroencephalograms were reported as being "within the range of normal variation" (Dr. Robert Cohn). Occasional waves of long duration were observed in the monopolar derivations.

At the time of this report the condition of the patient was essentially unchanged. He appeared to have recovered from the depression completely.

COMMENT

Briefly summarized, the psychiatric picture was one of severe cerebral degeneration. Intellectual deterioration precluded a more accurate analysis of the coexisting aphasia than the description of it as a mixed receptive-expressive defect, probably of a "transcortical"⁶ character. Apraxia was apparently ideomotor in type.

The presence of atopognosia and astereognosis and loss of position and vibratory sensations were striking. These abnormalities, plus the inability of the patient to calculate or write normally, his confusion of right and left and his misidentification of fingers, were indicative of large lesions in the parietal lobes. The last-named signs have been grouped together by Gerstmann⁷ as a syndrome, and are usually associated with involvement of the angular gyrus and the middle occipital convolution.

Pallor of the optic nerve heads may have been the result of ischemia. The weakness of the lateral rectus muscle is explicable perhaps on the basis of nuclear injury or compression of the abducens nerve during the time when the intracranial process was most acute. Partial severance of the left recurrent laryngeal nerve or tamponade by extravasated blood probably produced the defect in vocalization. The "ulnar palsy" was undoubtedly the result of the incision of the wrist.

It would seem that a combination of massive loss of blood and rapid fall in blood pressure could best account for the lesions underlying the neuropsychiatric syndrome. Air embolism may have been implicated, but the general extent of the clinical signs and the absence of convulsive seizures tend to eliminate this from consideration as an etiologic agent. The exact nature of the implied pathologic alterations is conjectural. The lesions present were thought to be of two types. The intellectual debilitation, confusion, disorientation and failure of memory could be correlated reasonably with the kind of diffuse necrobiotic changes in the cortex produced by Gildea and Cobb¹ in the experimental animal and

6. Nielsen, J. M., and FitzGibbon, J. P.: *Agnosia, Apraxia, Aphasia*, Los Angeles, The Los Angeles Neurological Society, 1936.

7. Gerstmann, J.: Syndrome of Finger Angnosia, Disorientation for Right and Left, Agraphia and Acalculia, *Arch. Neurol. & Psychiat.* 44:398 (Aug.) 1940.

observed at autopsy in the case of Schnedorf and associates.⁴ The neurologic abnormalities, the "transcortical" character of the aphasia and the existence of the Gerstmann syndrome indicate a more extensive injury in the parietal lobes of the brain. The encephalomalacia observed by Wolf and Siris,³ as well as Foix and associates,⁵ in whose patients injurious factors were similar, was predominantly parietal.

A word might be added concerning the rapid change in the patient's mood following his endeavor to end his life. Whether it was the attempt at suicide per se, sudden physiologic changes in the central nervous system induced by blood letting or subsequent lesions in the frontal areas, a sort of self-administered "shock therapy," or "lobotomy," appears to have been instrumental in the lifting of depression.

SUMMARY

A case of a suicidal attempt during involutional melancholia is reported. Severance of an external jugular vein almost resulted in complete exsanguination and death. Examination of the patient two months after the injury revealed evidences of extreme intellectual deterioration. The mood had changed to one of cheerfulness. A mixed receptive-expressive aphasia with a large semantic component and "transcortical" features existed. The patient was also apraxic. The principal neurologic signs were those associated with disease of the parietal lobes, and the Gerstmann syndrome was present. Diffuse cortical lesions of a focal ischemic character and larger infarcts induced by sudden cerebral anemia were thought to represent the pathologic substrate of the clinical picture. The possible relationship of the episode to the cessation of mental depression is commented on.

Saint Elizabeths Hospital.

News and Comment

COURSE OF STUDY IN THE RORSCHACH TEST IN DIAGNOSIS OF THE Milder MENTAL DISORDERS

The Michael Reese Hospital announces that Dr. S. J. Beck (Ph.D.) will offer his usual course this year on the Rorschach test. Accent will be on the less serious mental disturbances in which success in treatment appears possible. The differentiating patterns of responses to the test, for patients with such disorders, will be studied from full response records and will be contrasted with those obtained from patients with more serious conditions.

The course will be in session 2 two hour periods daily for five days, June 7 to 11, 1943, inclusive. Interested persons are invited to communicate with the Department of Neuropsychiatry, Michael Reese Hospital, 2908 Ellis Avenue, Chicago.

THE AMERICAN BOARD OF NEUROLOGICAL SURGERY

At a meeting of the American Board of Neurological Surgery, Chicago, Feb. 15 and 16, 1943, the following candidates passed the examination:

Samuel S. Allen, 3700 Fifth Ave., Pittsburgh; Capt. William F. Beswick, Medical Corps, Army of the United States; * Capt. Howard A. Black, Medical Corps, Army of the United States; Floyd H. Bragdon, Mercy Hospital, Pittsburgh; Bernard S. Brody, 107 Whitney Ave., New Haven, Conn.; Major Fritz Cramer, Medical Corps, Army of the United States; * Raymond M. P. Donaghy, Massachusetts General Hospital, Boston; Frederick A. Fender, 2361 Clay St., San Francisco; Harry E. LeFever, 9 Buttrick Ave., Columbus; * Frank E. Polmeteer, Mayo Clinic, Rochester, Minn.; James L. Poppen, 605 Commonwealth Ave., Boston; Lieut. Comdr. Robert H. Pudenz (MC), U.S.N.; * Lieut. Theodore B. Rasmussen, Medical Corps, Army of the United States; * Charles Robert Watson, 1014 Doaghey Bldg., Little Rock, Ark.; * Capt. Thomas A. Weaver, Medical Corps, Army of the United States; * John E. Webster, 840 David Whitney Bldg., Detroit; Major Barnes Woodhall, Medical Corps, Army of the United States, and Ward W. Woods, University Hospital, Ann Arbor, Mich.

* Certificates will be issued after fulfillment of a two year practice requirement.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

SOME OBSERVATIONS ON EARLY HUMAN FETAL MOVEMENTS. JAMES E. FITZGERALD and WILLIAM F. WINDLE, *J. Comp. Neurol.* **76**:159 (Feb.) 1942.

Fitzgerald and Windle studied 15 human fetuses between 7 and 9 weeks of gestation (18 to 26 mm. crown-rump length) under various operating conditions. Regardless of the type or strength of stimuli used, no fetal movements of a reflex nature could be elicited from the 6 specimens during a general anesthetic, after preoperative administration of morphine or after injection of solution of posterior pituitary U. S. P., or from the 6 fetuses delivered after procaine anesthesia, preceded by morphine or solution of posterior pituitary. Three specimens observed at operations performed with the mother under spinal anesthesia and with no preoperative medication reacted to appropriate stimulation. Continuous motion picture records of the experiments were made. The estimated age of the responding fetuses was 54 to 58 days (22.5 to 26 mm. crown-rump length). The responses were of two types. While the fetus was receiving oxygenated blood the excitability was high. After anoxia had set in a lateral movement of the head and trunk followed stimulation of the parts of the face supplied by the fifth nerve. The fetal muscles retained excitability long after all reflexes had disappeared.

ADDISON, Philadelphia.

SOME CONSIDERATIONS OF THE ELECTROENCEPHALOGRAM IN THE "CONVULSIVE STATE." B. L. PACELLA and S. E. BARRERA, *J. Nerv. & Ment. Dis.* **96**:125 (Aug.) 1942.

In all studies of the electroencephalographic changes associated with convulsive shock therapy produced either by metrazol or by the electric current the development of slow, 2 to 4 cycle per second waves of moderate to high voltage, appearing either at random or in a continuous series for interrupted periods, have been described. The persistence of abnormal records of this type, which closely resembled those seen in the cryptogenic convulsive states, depended roughly on the number of treatments the patient had received. None of the patients showed a pathologic record prior to therapy; in none was there a family history of epilepsy, and in no case was there any semblance of a petit mal attack occurring at the time the abnormal potentials were being recorded. Thus, the "paroxysmal cerebral dysrhythmia" can be considered as directly attributable to the shock treatment and as due either to the passage of the electric current through the brain or to the changes associated with the convulsion itself. The evidence favors the latter hypothesis and raises the question whether the pathologic electroencephalogram observed in cases of epilepsy can also be considered as due to changes induced by the convulsion itself, rather than to the etiologic factors in the disease. However, the occurrence of pathologic brain waves in relatives of epileptic persons, as well as in patients suffering only from petit mal attacks, is against this view. The assumption that a hyperirritable cortex in epileptic patients is revealed by the electroencephalogram is not supported by the fact that a higher voltage is usually necessary to produce a generalized convulsion in successive treatments by electric shock. Also, in 6 epileptic patients experimentally subjected to electric shock, the voltage necessary to produce a generalized convulsion was within the same range as that required for psychiatric patients with a normal pretreatment electroencephalogram. It was noted, however, that after one electrically produced convulsion each of the epileptic patients

exhibited an increased incidence of grand mal and petit mal seizures in the next few days. Thus, the possibility of altering "latent epilepsy" to clinically manifest epilepsy by shock treatment must be considered.

CHODOFF, Langley Field, Va.

CHANGES IN NORMAL ELECTROENCEPHALOGRAM OF MACACA MULATTA WITH GROWTH. MARGARET A. KENNARD and LESLIE F. NIMS, *J. Neurophysiol.* 5:325 (Sept.) 1942.

In the infant monkey cortical potentials began to develop at or before birth but were not well demarcated until three or four weeks after birth. From that time until the end of the sixth month there were progressive development and elaboration of the electroencephalogram until it resembled that of the adult. Frequency of waves was about 2 to 3 per second immediately after birth and increased to about 7 to 8 per second during the first six months and then slowly to about 10 to 12 per second by the end of the second year. The amplitude was low at birth, increased during the first six months and then slightly decreased. During the growth period the electroencephalogram became at once more complex and more uniform. There were less variations in the base line and in the type of potential. The effect of sleep could be detected in the older animals, but in the newborn infant fluctuations in the state of waking or sleeping were too slight and gradual to be correlated with the marked fluctuations in the type of the electroencephalogram, which may, however, be related.

The changes in the development of the infant monkey were like those described for man and were, as far as was known, coincident with the anatomic and functional development of the cerebral cortex.

ALPERS, Philadelphia.

EFFECT ON ELECTROENCEPHALOGRAM OF LESIONS OF CEREBRAL CORTEX AND BASAL GANGLIA IN MACACA MULATTA. MARGARET A. KENNARD and LESLIE F. NIMS, *J. Neurophysiol.* 5:335 (Sept.) 1942.

Lesions were made in the cerebral cortex and the basal ganglia of 41 monkeys, and electroencephalograms were recorded before and after operation. In every instance there was a temporary change in the electroencephalogram which appeared during the first or second postoperative day and consisted of flattening and slowing of the waves of medium frequency. The change was transient, was independent of the specific area injured but was more pronounced after larger lesions. In acute experiments with the animal under dial anesthesia, lesions of the cortex or of the basal ganglia produced no change in the electroencephalogram. After lesions restricted to the cerebral cortex there was no significant change in the electroencephalogram except the transient one already described. There was no focal effect of lesions of the cortex, and usually none following combined lesions of the cortex and the basal ganglia. In a few instances focal epilepsy could be observed. A lesion of the head of the caudate nucleus or of the putamen or of both was followed by pronounced changes in the pattern of cortical potentials. Hypersynchrony of the 8 to 10 per second waves became intensified, and the 15 to 20 per second waves became less evident or vanished. Combined lesions of the motor areas of the cortex and the basal ganglia caused the most decided changes. Hypersynchrony appeared and persisted for as long as two years. True epilepsy, evident both clinically and in the electroencephalogram, was found in 5 out of 15 animals. All the lesions which caused alterations in the electroencephalogram produced the most extreme changes in those animals which had been operated on in infancy.

ALPERS, Philadelphia.

CEREBELLAR ACTION POTENTIALS IN RESPONSE TO STIMULATION OF PROPRIOCEPTORS AND EXTEROCEPTORS IN THE RAT. ROBERT S. DOW and ROBERT ANDERSON, *J. Neurophysiol.* 5:363 (Sept.) 1942.

Cerebellar action potentials in the rat were recorded from surface folia after stimulation of exteroceptive receptors by moving the hair on different regions of

the animal's body and of proprioceptive receptors by tapping the tendons of isolated muscles of the forelimb and the hindlimb. The lobules explored were the highest part of the culmen, the lobulus simplex, the folium and tuber vermis, the pyramis, the uvula, crus I and crus II of the lobulus ansiformis and the lobulus paramedianus. Of the lobules explored the pyramis showed the most consistent activity after proprioceptive stimulation and the culmen after exteroceptive stimulation. There were marked differences in distribution of the responses, depending on which type of stimulation was used. Some of the potentials might have resulted from activity caused by intracerebellar connections. No consistent differences in the distribution of the responses were detected when different parts of the animal's body were stimulated. Because of the small size of the cerebellum, the rat was not the most suitable animal for this study. In respect to the cerebellar lobules activated, electrical stimulation of the sciatic nerve resembled exteroceptive stimulation more closely than proprioceptive stimulation. The distribution of activity throughout the cerebellum following electrical stimulation of the sciatic nerve in the rat was more widespread than in the cat, and much more so than in the monkey.

ALPERS, Philadelphia.

NEUROGENIC VESICAL DYSFUNCTION. C. E. JACOBSON JR., Proc. Staff Meet., Mayo Clin. 17:286 (May 6) 1942.

Jacobson produced neurogenic vesical dysfunction experimentally in female dogs by section of the pelvic and hypogastric nerves, by differential section of the sacral nerve roots and by transection of the cauda equina and the spinal cord. "The changes occurring in vesical tone and vesical capacity were recorded by means of preoperative and postoperative cystometrograms while the concomitant changes in the upper part of the urinary tract were recorded by means of excretory and retrograde urograms. Alterations of the appearance of the bladder were noted by cystoscopic examination."

Three distinct types of neurogenic vesical dysfunction of the spinal cord were observed to occur as a result of experimental lesions involving the peripheral nerve supply of the bladder and the spinal cord. These were (1) the atonic bladder, (2) the autonomous bladder and (3) the automatic, or reflex, bladder.

The atonic bladder is characterized by decreased vesical tone, increased vesical capacity and the complete absence of signs of vesical contractions. Urographically, there may or may not be dilatation of the upper part of the urinary tract. Cystoscopically, the bladder appears to be dilated and to have thin walls, elongated ureteral orifices and a wide-gaping vesical neck. The atonic bladder probably develops as a result of chronic overdistention due to the loss of normal transmission of sensory impulses from the bladder to the spinal cord.

The autonomous bladder is characterized by increased vesical tone, decreased vesical capacity and the presence of autonomous vesical contractions. Urographically, there is usually dilatation of the upper part of the urinary tract. Cystoscopically, there is evidence of hypertrophy of the vesical mucosa and muscularis, as well as relaxation of the vesical neck. The autonomous bladder probably develops as a result of loss of the normal motor innervation, a loss which permits the intrinsic nerve plexus of the bladder to function independently of the nervous system.

The automatic, or reflex, bladder is characterized by increased vesical tone, decreased vesical capacity and the presence of automatic, or reflex, vesical contractions.

ALPERS, Philadelphia.

Neuropathology

PATHOLOGIC CHANGES IN THE BRAINS OF DOGS GIVEN REPEATED ELECTRICAL SHOCKS. KARL T. NEUBUERGER, RICHARD W. WHITEHEAD, ENID K. RUTLEDGE and F. G. EBAUGH, Am. J. M. Sc. 204:381 (Sept.) 1942.

The authors induced convulsions in a series of 12 mongrel dogs by application of an alternating current. Shocks were applied at a potential of 80 volts and a current strength of 200 milliamperes; the duration of the individual shocks was

fifteen-hundredth second. Some of the animals died during the experiment. The others were killed by bleeding under anesthesia induced by soluble pentobarbital. The neuropathologic studies revealed that the cortex was more involved than the extracortical gray matter. The nerve cells showed rather widespread damage, including tigrolysis, paleness, swelling, vacuolation and in some instances even ischemic and "severe" changes. Satellitosis and neuronophagia were observed occasionally. Although the changes described in the brain are pathologic, they are not to be regarded as serious. Most of the nuclei of the nerve cells remained fairly well preserved. The variation in the degree of involvement may well be influenced by variation in individual susceptibility and by the degree of severity of the convulsions. The authors conclude that histologic changes induced by electrical shock in the brains of dogs are somewhat less severe than the changes observed after metrazol.

MICHAELS, Boston.

CEREBRAL LESIONS FOLLOWING ADMINISTRATION OF NEOARSPHENAMINE. CYRIL B. COURVILLE and CLEMON MARSH, Arch. Dermat. & Syph. **46**:512 (Oct.) 1942.

Courville and Marsh report an unusual and hitherto unstudied lesion of the brain, which they designate as multiple symmetric foci of hemorrhagic necrosis, which constitutes an integral part of the encephalitis syndrome following intoxication with neoarsphenamine.

The lesion is closely allied to pericapillary encephalorrhagia in that it is composed of many perivascular hemorrhages, which in this case are grouped into circumscribed areas, in contrast to their otherwise diffuse spread throughout the white matter of the brain.

The basis for the study was a series of 12 cases of encephalitis due to arsphenamine in which the cerebral lesions were observed at autopsy. In 7 cases multiple symmetric foci of hemorrhagic necrosis were observed (in 1 case, both grouped and scattered petechial hemorrhages were present); in 4 other cases typical petechiae were scattered throughout the white matter, while in 1 case gross hemorrhage into the brain had taken place. Any combination of these three lesions may exist.

One feature of special interest was the tendency of the hemorrhagic foci to localize in regions of both the gray and the white matter of the brain. The corpus callosum, the optic thalami, the external capsule and the frontal and parieto-occipital centricums (forceps minor and forceps major) seem to be sites of predilection.

The further tendency of the lesion to occur in symmetric areas of the brain suggests some functional vascular basis for its occurrence. The focal blood vessels supplying these areas are evidently susceptible to the toxic agent to the same degree at the same time. While the lack of epinephrine may enter into this situation, as Ehrlich originally postulated, one can be more sure that dilatation of the blood vessels (arterioles) predisposes them to involvement by the toxic process.

Like disseminated petechial hemorrhages, the lesion is not necessarily fatal, as a case in which there was a rather long survival period indicates, although it must produce serious clinical residuals if at all widespread or severe.

The lesion should be considered a pathologic entity which with disseminated petechial hemorrhages and the rare gross cerebral hemorrhage constitutes one of the essential pathologic elements resulting in the clinical syndrome of post-arsphenamine hemorrhagic encephalitis. The occurrence of localizing or lateralizing clinical phenomena in a clinical case should suggest the occurrence of this lesion.

ALPERS, Philadelphia.

TRAUMATIC HEMORRHAGE INTO THE PITUITARY GLAND. R. A. MUNSLOW, J. L. HAYMOND and A. S. CRAWFORD, Arch. Path. **34**:431 (Aug.) 1942.

The authors report the case of a man aged 35 with a history of trauma to the head, followed by unconsciousness and death three and one-half hours later.

Autopsy revealed basal fractures of the skull with lacerations of both frontal and temporal lobes in their inferior portions. Scattered hemorrhages, measuring up to 6 mm. in diameter, were observed in the gray and white matter of the cerebrum, especially in the tegmentum pontis. Hemorrhages were seen also in the posterior lobe of the pituitary gland.

WINKELMAN, Philadelphia.

LISSAUER'S DEMENTIA PARALYTICA. A. J. GALBRAITH and A. MEYER, *J. Neurol. & Psychiat.* 5:22 (Jan.-April) 1942.

Galbraith and Meyer report the case of a woman aged 40 who showed predominantly psychotic reactions for about six years before organic manifestations became apparent. The latter consisted of Argyll Robertson pupils, a Korsakoff-like syndrome and atypical serologic responses consisting in a negative Wassermann reaction and a colloidal gold curve characteristic of dementia paralytica. Examination elicited focal signs, such as left hemianopia, disturbance in visual attention, constructional apraxia, drawing disturbance, finger agnosia, inability to distinguish right and left, agraphia and acalculia. The signs pointed to lesions in the parieto-occipital region and suggested a diagnosis of Lissauer's dementia paralytica. This was confirmed by the pathoanatomic observations, which, though diffuse, were most intense in the occipital lobes. Here, in spite of absence of macroscopic atrophy, there were intense infiltrations, with invasion beyond the pia-glia membrane, disintegration of the cortical tissue, presence of numerous "plump" cells and foci of demyelination and unusually severe inflammation of the white matter. These changes are regarded by the authors as an early and "pre-spongiosus" phase of Lissauer's type, before atrophy or the status spongiosus, regarded as essential to this form, has developed. Pathogenetically, the case tends to confirm the original views of Lissauer and Alzheimer that the circumscribed lesions are the expression of a local intensification of the process and are not due to extraneous factors. The failure to demonstrate spirochetes in this and in other cases of Lissauer's form of dementia paralytica should not be regarded as absolute proof that spirochetosis is not responsible for the lesions.

N. MALAMUD, Ann Arbor, Mich.

OCULOLARYNGOPHARYNGOVELOPALATIVE MYOCLONIA IN A BULBOPONTILE SYNDROME.

C. JAKOB and JUAN C. MONTANARO, *Rev. neurol. de Buenos Aires* 7:85 (April-June) 1942.

Jakob and Montanaro give an account of a 35 year old man who suddenly was taken with a pain at the left angle of the mouth, was dizzy and vomited. Peripheral paralysis of the left side of the face and paresis of the right limbs developed rapidly. The patient was syphilitic. He was found on examination to have paresis of the left sixth nerve and paralysis of the left fifth and seventh nerves, right hemiparesis, anesthesia of the left side of the face and right hemihypesthesia. In addition, there was myoclonia of the palatal, pharyngeal, laryngeal and ocular muscles. He died about three years after the attack. Careful examination of the brain revealed a focus of degeneration in the left side of the tegmentum involving the nuclei of the cranial nerves from the fifth to the eighth. The fifth and seventh nerves were completely interrupted; the eighth, only partly. The following pathways were involved: the median and lateral fillets, the tract of Gowers, the central tegmental tract, the middle cerebellar peduncle and the greater part of the left reticular formation. The temporopontile and the pyramidal tracts were partially destroyed. In addition, the nuclei of the reticular formation, the superior olive, the cerebellar root of the vestibular nerve, the floccular peduncle in part and the mesencephalic root of the trigeminal nerve were destroyed. The authors conclude that velopalatine myoclonia is not due necessarily to a circumscribed focal lesion but is the functional result of an alteration of the total equilibrium of paleodentato-olivary systems.

BAILEY, Chicago.

PATHOGENESIS AND HISTOPATHOLOGY OF HYDROPHOBIA IN MAN. ISTVÁN TARISKA, *Deutsche Ztschr. f. Nervenhe.* **152**:133 (May) 1941.

Tariska reports on the histologic changes in the brains of 2 children, each aged 9 years, who died of hydrophobia. In the first child the bite was on the left cheek; the patient received antirabic inoculations. Pathologically the case was characterized by severe inflammatory changes in the medulla and pons, with the greatest intensity of the reaction in the neighborhood of the hypoglossal nucleus. The inflammation was greater on the left side than on the right. The gasserian ganglion was involved on both sides, but the substantia nigra was unaffected.

In the second child the bite was on the right lower extremity; this child failed to receive antirabic inoculations. There were intensive changes in the intervertebral ganglia, the lumbosacral portion of the cord and the substantia nigra.

The author concludes that his cases do not support either the theory of Schaffer that the virus spreads through nerve pathways or the theory of Schükrü and Spatz that it is disseminated by way of the cerebrospinal fluid. He thinks it more likely that the virus spreads by way of the spinal ganglia and the sympathetic nerve chain.

MERRITT, Boston.

MICROGLIOMA. LADISLAUS BENEDEK and ADOLF JUBA, *Deutsche Ztschr. f. Nervenhe.* **152**:159 (May) 1941.

Benedek and Juba report a case of a rare type of primary tumor of the brain, a microglioma. In a man aged 34 there developed over a span of four to five weeks headache, failing vision, aphasia, right hemiparesis and olfactory hallucinations. Examination revealed papilledema, amnesic aphasia and visual verbal agnosia and right hemiparesis, with increased reflexes and a Babinski sign. Necropsy revealed a large infiltrating, yellowish pink tumor of the left temporoparietal lobe. Histologically the tumor was very cellular and was composed principally of microglia cells, which stained specifically by Penfield's combined method. The only macroglia cells were in the white matter adjacent to the tumor. Connective tissue stains revealed a delicate mesh of reticulum, particularly around blood vessels.

It is the authors' contention that the tumor which they record was a true microglioma and that the microglia cells seen in the tumor were not scavenger cells in areas of necrosis. In support of this thesis are the facts that the microglia cells were the only elements present and that they were distributed evenly throughout the tumor, rather than around blood vessels and in necrotic tumor tissue.

ADAMS, Boston.

Psychiatry and Psychopathology

DETERIORATION OF PATIENTS WITH ORGANIC EPILEPSY. ALEX J. ARIEFF and G. K. YACORZYNSKI, *J. Nerv. & Ment. Dis.* **95**:49 (July) 1942.

Arieff and Yacorzynski studied 27 patients with organic epilepsy by means of the Stanford-Binet test over a period of several years to determine whether and to what extent deterioration occurs. The patients, who suffered from such conditions as craniocerebral trauma, infections, tumor, vascular disease and chronic alcoholism, were tested at intervals of one to nine years. As a group there was a decrease of 6 in the intelligence quotient between the first and the final test—a significant shift. A control group of epileptic patients without demonstrable cause for their seizures failed to show a general deterioration. In 37 per cent of the original group of patients there was a significant decrease in intelligence scores, in contrast to approximately 6 per cent of the control group who showed a decrease.

CHODOFF, Langley Field, Va.

THE PSYCHOPATHOLOGY OF THE EGO SYSTEM. GEORGE W. KISKER and GEORGE W. KNOX, *J. Nerv. & Ment. Dis.* 95:66 (July) 1942.

Kisker and Knox undertake to apply the gestalt concept of the ego system to mental disorder. In gestalt psychology, the behavioral field is the field of experience or consciousness viewed in terms of dynamics or postulated forces. Mental development is the process of differentiation of the behavioral field from the state of homogeneity existing in infancy to a state of heterogeneity. The "things," or behavioral objects, which emerge in this process organize, influence each other and further articulate within themselves. The ego, as one of these objects, becomes abnormal if there is excessive or deficient ego emergence, ego articulation or ego relationship to other objects.

The ego, which is the most important part of the total field of experience, differs from the behavioral objects in that it serves as the axis and core of the behavioral field. The ego in its development goes through definite stages: (1) The "non-I" stage, in which the ego is at first undifferentiated from its environment; (2) the "I" stage, in which the ego later differentiates itself from its environment and articulates within itself; (3) the "my" stage, in which the ego incorporates other behavioral objects under its sphere of influence, and (4) the "we" stage, in which the ego becomes a subordinate of a larger group.

Mental abnormalities occur with various deviations from, or blocking of, these stages of ego development. These may take the form of regression to earlier stages, in which the individual becomes unable to distinguish himself from his surroundings. Splitting of the ego subsystems results in dual or multiple personality. If the ego is unstable or inadequate, it may attempt to achieve stability either by the expanding of material possessions or, if this is impossible, because of constraining geographic situation, by constructing an expanded framework for the ego system, with resulting grandiose delusions. The first type of reaction produces a dictator and the second a psychotic person, but there is no real difference between them.

CHODOFF, Langley Field, Va.

ON THE FEAR OF BEING BURIED ALIVE. SANDOR FELDMAN, *Psychiatric Quart.* 16:641 (Oct.) 1942.

The idea "What if I should be buried alive?" is of great importance to both children and adults and occurs frequently. It creates depression, distracts attention from the social tasks of life and may arrest physical and mental development. It is often the sole cause of night terrors. It disturbs sleep.

In adults, the obsessional idea makes an indelible impression on the whole personality, disturbing normal activity and leading to compensations and reactions against the dreaded possibility. It may appear in the fantasies of early childhood. The whole waking life is obsessed with the fear, but it usually takes possession of the mind at night when the sufferer goes to bed.

In some cases moral discontentment was found to be responsible. A person is "dead" although physically alive if he cannot respect himself; he is "buried alive" if he cannot live up to his moral and ethical ideals. The author also presents evidence to show that the obsessional idea may be a desire on the person's part to be buried alive and to be dug out of the grave in order to have reunion with his parents.

In everyday language the expression is often heard and used, "You do not exist for me," "you are a dead man for me," if a person feels resentful and threatens another with the withdrawal of love. When a person is not loved by a dear one, when he does not count, he feels as if he were dead.

Not to be loved or not to love is expressed by the fear of being buried alive. It explains also the fear of death itself. Only he who loves and is loved feels he is alive and is not concerned with death. Not thinking of death, he is not afraid of it, even in old age. As is well known, the desire to repeat the experience of being in the mother, in the womb, where he was buried alive and yet connected

with the world and taken care of, also returns regressively in the fear of being buried alive and in the fantasy of arranging some kind of communication with the loved ones while alive in the ground.

LESKO, Bridgeport, Conn.

THE SUCCESSFUL TREATMENT OF A CASE OF ACUTE HYSTERICAL DEPRESSION
BY A RETURN UNDER HYPNOSIS TO A CRITICAL PHASE OF CHILDHOOD.
MILTON H. ERICKSON and LAWRENCE S. KUBIE, Psychoanalyt. Quart. **10**:
583, 1941.

In a woman aged 23 there suddenly developed a rapidly progressive and deepening depression. Both extrainstitutional psychiatric treatment and psychoanalysis were tried, but no improvement was obtained. Her friends reported that she was raised in a very moralistic family. When she was 13 years old her mother died. At 20 years of age she and her best friend fell in love with the same man, who married her friend. The next year the friend died, after which the man returned and renewed his acquaintance with the patient. After a date with him she returned depressed, disgusted and nauseated. From that point her illness began. The man stated that he had proposed marriage; she had accepted, but when he was about to kiss her she vomited over him.

As any approach by psychiatric or psychoanalytic technics had failed, and as these attempts had made her worse, it was decided to try hypnosis. The approach had to be indirect, for it was feared that the results of a direct approach might be serious. An arrangement was made to have her attend as a chaperone the hypnotic treatment of a friend. She was hypnotized without her knowledge. At the first session she was induced actually to regress to an age between 11 and 13 years and to report her mother's restrictive advice about sexual matters. With this advice the therapist agreed, simply raising the question whether the mother would not have instructed her further as she grew older. At the second session the events of the previous session were reviewed silently by the patient and then reported. It was again brought to her attention that her mother had died before she had a chance to finish her sexual instruction. At the third session the patient was told to repress all memories of the other sessions except the first posthypnotic story of her mother's sex instructions. Then both while she was under hypnosis and after hypnosis she was asked to consider what she thought her mother's further instructions would have been had she lived. This treatment resulted in a complete cure, with a change in her attitude toward men and ability to have dates and to marry the widower. Two years later she was still well and was happy with her husband and baby.

The procedure in this case was interesting. The therapist agreed with the patient's oversevere superego and modified it only in the light of growth from childhood to adulthood. The therapist also ordered the patient to suppress all but the most rudimentary insight. Treatment was started in an indirect way. The authors mention a number of questions raised by the case and the possibility in some cases of altering rigid psychoanalytic technic along similar lines.

PEARSON, Philadelphia.

A STUDY OF STRUCTURAL AND INSTINCTUAL CONFLICTS IN CASES OF HAY FEVER.
G. W. WILSON, Psychosom. Med. **3**:51 (Jan.) 1941.

Wilson discusses the significance of material obtained from the psychoanalytic study of 7 cases of hay fever. He concludes that the psychogenic aspect of hay fever is a result of unsuccessful olfactory repression. Frustrated sexual curiosity early in life seems to be a primary factor in producing this unsatisfactory repression, with resultant displacement of interest to the physiologic function of elimination. All the patients in the series recalled childhood seductive experiences involving parental interest in excrement. Sensitivity to odors indicative of relatively increased olfactory perception was elicited in all patients. The dreams of 1 patient demonstrated the displacement of sexual curiosity and affective interest from the visual to the olfactory sphere. The author believes that unsatisfied olfactory sexual curiosity may be considered as a constant irritant to the nasal

mucous membrane. This internal psychogenic factor may be more or less important than the external pollen factor in various patients, and either may be sufficient to precipitate an attack of rhinitis.

SCHLEZINGER, Philadelphia.

ALCOHOLISM AND MENTAL DISORDER. JACKSON M. THOMAS, *Quart. J. Stud. on Alcohol* 3:65, 1942.

Thomas reports 5 cases to illustrate the multiplicity of factors which may be involved in the genesis of alcoholism. Many of the statistics in the past have ignored the complexity of the question and reflect largely the personal bias of the investigators. No general formula fits all cases, and each patient must be regarded as an individual problem who uses alcohol in his own peculiar way to assist in his efforts to adjust in life. Likewise, the more or less direct results from the use of alcohol vary greatly in different persons and under different circumstances.

DRAYER, Philadelphia.

THE APPLICATION OF THE RORSCHACH TEST TO A SAMOAN GROUP. P. H. COOK, *Rorschach Research Exchange* 6:51 (April) 1942.

The subjects were 50 students from a mission high school, where boys are trained to become native pastors. The mean age was 20.6 years. Though these boys may not be representative of true Samoans, they represent a genuine non-European cultural and racial group. All the boys came from the higher-ranking families and were above the average Samoan in ability and development.

The tests were given in Samoan by an interpreter. The primary purpose was to see how a non-European cultural group reacted to the Rorschach test and what could be elicited from such a group on the basis of the Rorschach theory. A few of the results follow: There was overemphasis on whole responses, which were simple and crude. The author feels that this manner of approach may be explained by the fact that the language and the level of development of the Samoan social pattern are far below that of other Rorschach subjects. Also, the Samoan's ambition exceeds his ability.

There was a large usage of white space (S). The reason for this, the author explained, may be the strong influence of the missions and the white men on these particular Samoans. Few determinants other than form (F) were used. Although this is usually a sign of a compulsive or depressive rigidity, here it might be due to the fact that the Samoans expect and accept a certain form of rigidity and compulsion. M responses were few, the FM type being used twice as often as the M type. In Samoans this does not necessarily mean emotional immaturity. To the Samoans, belief in spirits and a fear and anxiety for certain things are natural. Therefore the large use of k, K and FK responses is not startling. The small number of texture responses may be attributed to the lack of differentiation in personality and perception, as well as to an unfamiliarity with most objects referred to in common texture responses, such as "fur" and "rug." CF and pure C responses were much greater than FC responses, which may be explained, the author states, by the fact that the colors of the tropics are simple and harsh and the Samoans have developed little sensitiveness to color nuances. Although the choice of content was limited and stereotyped, there are two explanations for this: First, in intelligence the Samoan group would fall below an average American group; second, the opportunity for development is limited in the tropics. When voting for the most and the least preferred cards, the colored cards were the most preferred and card V was the least preferred.

A comparison of the differential data on the subjects, as presented by the schoolmasters, with the results of the Rorschach test were not satisfactory, primarily because the data given on the subjects were influenced by the preferences of the teachers and were not, therefore, altogether true. However, the Rorschach test can and should be applied to non-European cultural groups.

MARCOVITZ, Philadelphia.

Diseases of the Brain

THE INHERITANCE OF DIABETES INSIPIDUS. HARRY BLOTNER, *Am. J. M. Sc.* **204**:261 (Aug.) 1942.

Blotner reports a case of diabetes insipidus in a man whom he had observed for five years; the mother and grandmother also suffered from the disease. The patient was 25 years old and unmarried. As soon as he could walk and reach for water, it was noticed that he drank all that he could get. As he grew older, he imbibed as much as 3 or 4 gallons (11 or 15 liters) of water a day. His daily fluid intake and output had been about 10 to 12 liters. Solution of posterior pituitary U. S. P. administered intramuscularly or intranasally reduced the polyuria and polydipsia to normal. The patient's mother, a widow aged 50, had consumed much water since childhood, and up to the age of 10 years she always took a quart (946 cc.) or more to bed with her. The condition improved at the time of her menopause, and she takes now about 5 to 6 liters of fluids daily. The grandmother imbibed 2 gallons (7.5 liters) of water a day when she was a girl. She, too, improved at the time of her menopause but still had polyuria and polydipsia at the age of 64, when she died of heart disease.

The records of 70 patients revealed only these instances of familial diabetes insipidus. The disease may be inherited through the maternal or the paternal side and transmitted either to male or to female children. There is general impression that familial diabetes insipidus is due to a dominant gene.

MICHAELS, Boston.

NARCOLEPSY. HENRY G. HADLEY, *J. Nerv. & Ment. Dis.* **95**:13 (July) 1942.

Narcolepsy is characterized by attacks of untimely sleep and by cataplexy. Cataplectic attacks are due to cortical inhibition, and Pavlov expressed the belief that narcolepsy is due to excessive inhibitability of the cerebral cortex. Narcolepsy may be a manifestation of disease of the infundibular system, and Redlich has pointed out the frequent association of endocrine dysfunction with the syndrome. The symptomatic forms are without cataplectic manifestations, while the primary type shows both features of the syndrome and is of cortical origin. The symptomatic type may appear in cases of epidemic encephalitic, cerebral trauma, tumors of the floor of the third ventricle and the aqueduct of Sylvius, multiple sclerosis, dementia paralytica and epilepsy. Hadley reports a case of primary narcolepsy with the later incidental development of a glioma.

CHODOFF, Langley Field, Va.

EARLY SYMPTOMS OF APHASIA WITH BRAIN TUMORS. MARK KANZER, *J. Nerv. & Ment. Dis.* **95**:702 (June) 1942.

Kanzer believes that in cases of aphasia associated with tumor of the brain the initial manifestation is likely to be difficulty in word finding. There has been considerable controversy in the literature as to whether amnesic aphasia represents a special type or a variation of other types of aphasia which may occur with a number of diffuse and local lesions of the brain. Weisenburg placed amnesic aphasia in a special category because of psychologic differences from the other types of aphasia. His 5 cases were observed only in patients suffering from brain tumor. He made no suggestions as to the localizing value of amnesic aphasia.

The studies of Head included 5 cases of nominal aphasia, a term which undoubtedly corresponds to amnesic aphasia. All occurred in association with a mild cerebral lesion or during recovery from a more serious disorder.

Goldstein, who was concerned chiefly with the psychologic aspects of the disorder, expressed the belief that the diagnosis should be made only after detailed psychologic studies.

The author draws the following conclusions from the observations of the aforementioned investigators: 1. Amnesic aphasia is a mild disorder of speech, usually occurring in association with moderate trauma to the skull, during the early

stages of a tumor or during recovery from a vascular lesion or wound. 2. Pathologic studies have not yielded a clear conception of the localizing significance of the disorder. 3. Establishment of psychologic criteria for the diagnosis of amnesic aphasia has not led to a better understanding of its clinicopathologic background.

The author then turns to his own case material and states that the anamnesis usually reveals a characteristic picture marked first by "slight forgetfulness," which on close analysis is resolved into difficulty in using proper names or words as names of objects. When the patient is admitted to the hospital, examination usually gives the picture of a more advanced defect, in which the difficulty in naming objects appears to be part of a subtle, but more profound, intellectual and personality disturbance. In some cases the speech difficulties have gone beyond the stage of pure amnesic defect and there is an admixture with the signs of early sensory aphasia.

The localizing value of amnesic aphasia has been the subject of much debate. It remains inconclusive in spite of the claims of Kleist that the disturbance is associated exclusively with a lesion of the posterior part of the second and third temporal convolutions. The author believes, with Henschen, that amnesic aphasia may occur as an early symptom with lesions of various portions of the brain and that it represents a mild manifestation of true aphasia in the sense of Goldstein.

The author divides his cases into two groups: (a) those in which the aphasia appeared simultaneously with, or after, involvement of the right upper extremity and (b) those in which the occurrence of amnesic aphasia preceded the involvement of the right upper extremity. In the first group the lesion is believed to be anterior, the defect being akin to the early stages of typical Broca's aphasia, while in the second group the region of the posterior temporal and the parietal lobe is involved.

Two alternative theories are offered to account for these observations: 1. Amnesic aphasia may be regarded as a disturbance in language which is produced by disruption of the association pathways between the sensory and the motor centers of speech. 2. Amnesic aphasia may be considered as the result of an early lesion involving an extensive common language zone about the fissure of Sylvius, with loss of association functions.

CHODOFF, Langley Field, Va.

TRIGEMINAL NEURALGIA AND TUMORS OF THE GASSERIAN GANGLION. J. G. LOVE and H. W. WOLTMAN, *Proc. Staff Meet., Mayo Clin.* **17**:490 (Sept. 9) 1942.

Love and Woltman report 2 cases of tumor of the gasserian ganglion occurring in patients suspected of having typical trigeminal neuralgia. They comment on the rarity of tumors of the gasserian ganglion and call attention to the fact that in cases of trigeminal neuralgia with lack of freedom from pain between paroxysms tumor of the gasserian ganglion should be suspected.

ALPERS, Philadelphia.

HEREDODEGENERATIVE CEREBELLAR DISORDERS. ANTONIO R. DE MELLO, *Arch. brasil. de med.* **32**:109 (April) 1942.

After a brief history of the development of the present concept of the hereditary cerebellar disorders, Mello describes a case which he had the opportunity of studying clinically and pathologically. The observation concerns a woman whose disease began at about 29 years of age with unsteadiness of gait, which steadily progressed. Examination two months before death, at the age of 36, disclosed fixed facies, apathy, exophthalmos, slight ptosis, inability to walk, general muscular weakness and atrophy, especially in the distal parts of the lower extremities, slight asynergy on voluntary movement of the arms, a bilateral Babinski sign, exaggerated patellar reflexes and incontinence of feces and urine. The patient could scarcely speak even a few syllables and had great difficulty in swallowing.

She died of pneumonia. Several members of the family, representing at least three generations, had a similar complaint. Anatomic study revealed atrophy of the cerebellar cortex and sclerosis of the cerebellar tracts, the pyramidal tracts and the fasciculi of Goll.

The author offers this case in support of Austregesilo's thesis of the close relationship of Marie's cerebellar ataxia, Friedreich's ataxia and peroneal atrophy. He proposes to call the condition in his case spinocerebellar heredoataxia.

BAILEY, Chicago.

Treatment, Neurosurgery

AN ANALYSIS OF DEATHS FOLLOWING THERAPEUTIC MALARIA. UDO J. WILE and LESLIE K. MUNDT, *Am. J. Syph., Gonorr. & Ven. Dis.* **26**:181 (March) 1942.

Since 1925, 1,026 patients with neurosyphilis have been treated by inoculation with malaria at the University of Michigan Hospital. Wile and Mundt report their analysis of the causes of the 29 deaths. They suggest, in retrospect, that some of the deaths might have been prevented. This is particularly true since the advent of sulfonamide therapy, which might have prevented some of the deaths caused by infection. Sixty-six per cent of the 29 deaths occurred in patients with dementia paralytica, the highest mortality rate occurring in the older age groups.

The most frequent serious complication responsible for 12 deaths was sudden peripheral circulatory failure or vascular collapse. The signs and symptoms were those of true medical shock. The time and occurrence of the circulatory collapse were unpredictable, coming on at any period during treatment. The deaths of 5 patients were attributed, directly or indirectly, to extreme hyperpyrexia; 5 patients died as a result of pneumonia, while intercurrent acute infection, vascular accidents, internal hemorrhage and suicide (in 2 cases) accounted for the death of the others.

BECK, Buffalo.

USE OF ALPHA TOCOPHEROL IN THE TREATMENT OF NEUROMUSCULAR DISORDERS. ALBERT J. LUBIN, *Arch. Int. Med.* **69**:836 (May) 1942.

Lubin reports on the use of alpha tocopherol in large doses in 35 cases of neuromuscular disorders. At frequent intervals the patient's subjective impressions and quantitative measurements of their progress were obtained. Muscular strength was measured by dynamometric methods. Electrical reactions to faradic and galvanic currents were noted, and chronaxias were measured. Frequent determinations of the creatinine and the creatine output in twenty-four hours were performed. The patients consisted of four groups: (1) 7 with amyotrophic lateral sclerosis; (2) 9 with muscular dystrophy; (3) 5 with muscular atrophy of unknown cause, and (4) 14 with other diseases of the neuromuscular system.

The condition of 31 patients remained stationary or became worse during the period of treatment. In the 4 patients who showed improvement it was shown that alpha tocopherol was in no way responsible for the beneficial results. The method of study is suggested for use of other investigators of the problem of neuromuscular disorders.

BECK, Buffalo.

WARD THERAPY. NATHAN BLACKMAN, *Psychiatric Quart.* **16**:660 (Oct.) 1942.

Blackman describes a method of group psychotherapy characterized by passive guidance on the part of the therapist and active participation by the patient. The atmosphere is one of friendliness and impartiality. The patients present their own cases, and instructive discussions by the patient and other patients and the therapist are held. This method of ward therapy is presented as a means of utilizing available psychiatric guidance in the face of an ever increasing scarcity of medical personnel.

LESKO, Bridgeport, Conn.

THE TREATMENT OF BRAIN ABSCESS. D. W. C. NORTHFIELD, J. Neurol. & Psychiat. 5:1 (Jan.-April) 1942.

Northfield reviews his treatment of abscess of the brain in 31 patients and finds that of 12 patients treated by drainage only 3 lived, whereas of 19 patients treated by aspiration, decompression or enucleation alone or combined 11 survived. Thus closed methods of treatment offer a much more favorable prognosis than the open method. Failures are primarily due to such complications as multiple abscesses, massive edema or acute meningitis. Edema may be controlled in the early stages by dehydration therapy, but as a rule the best results are achieved by surgical decompression. When meningitis, including ventriculitis, is a complication of brain abscess it should be treated by decompression measures rather than by frequent lumbar punctures, since the latter tend to promote herniation. Chemotherapy doubtless combats meningitis, but not the abscess proper. Successful treatment depends on accurate localization and a diagnostic burr hole, tapping or ventriculography. The time of surgical intervention varies but should be resorted to whenever the clinical condition begins to deteriorate. Aspiration should be attempted first. This is followed by decompression only if tension is not sufficiently relieved, if there is considerable swelling of the brain or if the abscess is deep seated. At the time of aspiration, the cavity of the abscess should be irrigated with a 50 per cent electrolytic solution of sodium hypochlorite. Repeated aspirations may be necessary, but intervals will gradually lengthen. Injection of 1 to 2 cc. of thorium dioxide into the abscess may be of help in roentgenologic visualization of the organization of the wall of the abscess. Enucleation of an abscess depends on the formation of a well defined and tough wall. This optimum period varies, but the usual time is about the third month. Enucleation may prevent the occurrence of a convulsive disorder, and anticonvulsants should always be administered until the abscess is fully eradicated. Drainage should be used only in exceptional cases, such as those of infected compound fractures of the skull or superficial subdural abscess.

N. MALAMUD, Ann Arbor, Mich.

Encephalography, Ventriculography, Roentgenography

THE SIGNIFICANCE OF VERTEBRAL FRACTURES AS A COMPLICATION OF METRAZOL THERAPY. NORMAN L. EASTON and JOSEPH SOMMERS, Am. J. Psychiat. 98: 538 (Jan.) 1942.

Easton and Sommers studied the incidence of vertebral fractures in 200 patients both before and after metrazol therapy. They found a fracture incidence of 23 per cent, with a slightly greater frequency in males than in females. Age was a factor, since the fewest fractures occurred between the ages of 21 and 55, and the highest incidence occurred after the age of 55. The average number of vertebral fractures per patient was 2.4. All fractures occurred in the thoracic region, the greatest number involving the fourth, fifth and sixth thoracic vertebrae. All were confined to the bodies of the vertebrae, chiefly to the superior portion. In no case were the laminae or pedicles involved. Pretherapy roentgenograms in some cases showed kyphosis, scoliosis, arthritis, nuclear changes or old fractures. None of these conditions predisposed to the development of vertebral fractures. Roentgenographic examinations and determinations of calcium of the blood and spinal fluid carried out through the course of metrazol therapy gave no indication of a specific effect of metrazol on calcium metabolism. Moreover, no correlation between the mental status and the incidence of fractures could be determined. Easton and Sommers comment on the mild nature of the symptoms resulting from the fractures. Less than half of their patients complained of pain, and only 3 of the patients had recurrence of pain. The authors state that the most important aspect of therapy is prophylactic and recommend mechanical support of the spine during convulsions.

FORSTER, Boston.

ACQUIRED SUBTENTORIAL PRESSURE DIVERTICULUM OF A CEREBRAL LATERAL VENTRICLE. CORNELIUS G. DYKE, *Radiology* **39**:167 (Aug.) 1942.

Dyke states that no cases of the condition which he describes have been recorded in the literature, though there are numerous reports of cerebral defects due to other disturbances. An acquired subtentorial pressure diverticulum of a cerebral lateral ventricle is a condition in which part of the medial portion of a lateral ventricle extends medially and caudally through the tentorial incisura to exist as an accessory infratentorial, fluid-filled sac. It is important that this be recognized and that the diverticulum be not confused with a rostrally displaced fourth ventricle.

Three cases of the lesion are cited, 1 of which was verified at necropsy. The diagnosis was made in 2 instances from the pneumencephalograms. The first case was that of a young man who had had attacks of unconsciousness for five months. Roentgenograms of the skull showed a decided increase in intracranial pressure. Pneumencephalograms revealed conspicuous enlargement of the lateral and third ventricles and an unusually large collection of gas beneath the tentorium, which at necropsy proved to be a diverticulum of the left lateral ventricle. Case 2 was that of a woman aged 46, who had had paresthesias of the left side of the face and body for five years and sudden temporary paralysis of the left side of the body. Ventriculograms showed notable ventral depression of the lateral ventricles and a large collection of gas beneath the tentorium which undoubtedly represented a pressure diverticulum of the lateral ventricle. Case 3 was that of a 16 year old girl who complained of "loss of pep," headache, amenorrhea and diplopia. Great dilatation of the lateral and third ventricles and a moderate-sized diverticulum were demonstrated on ventriculographic examination. It is interesting to note that the author demonstrated the diverticulum in 2 of the cases by lamina-graphic studies of the air-filled ventricle.

The diagnosis of the condition is important, as the size and shape of the diverticulum are not unlike those of a greatly dilated fourth ventricle. It usually occupies a position too high for the fourth ventricle and in most cases is much larger than this structure.

The portion of the medial wall of the lateral ventricle to give way was apparently the hippocampal gyrus. The distance which the medial wall of the ventricle must migrate to reach the edge of the tentorium is negligible, for normally the medial margin of the atrium and the posterior third of the body of the lateral ventricle are practically in the same vertical plane as the free edge of the tentorium. This is true of the exact area where the hippocampus swings laterally from the thalamus, and the gyrus here is rather thin. Therefore when the lateral ventricles are enlarged, particularly when they are greatly dilated, the medial portion of the atrium of the lateral ventricle is actually medial to the free edge of the tentorium, thereby facilitating the formation of a subtentorial diverticulum.

The underlying cause of the subtentorial diverticulum in all the cases was pronounced elevation of the intracranial, especially the intraventricular, pressure. The nature of the wall of the diverticulum cannot be determined, but there is probably a thin layer of brain tissue and leptomeninges and the wall may well be lined with ependyma.

KENNEDY, Philadelphia.

THE ROENTGENOGRAPHIC APPEARANCE OF THE BONES IN CUSHING'S SYNDROME. MARCY L. SUSSMAN and BENJAMIN COPELMAN, *Radiology* **39**:288 (Sept.) 1942.

The clinical picture of Cushing's syndrome in the female, in whom most of the cases have been reported, consists of deposition of fat on the trunk, vascular hypertension, amenorrhea, purplish striae on the abdomen and thighs, choleric facies, various degrees of hirsutism, actiniform eruptions, decreased sugar tolerance and osteoporosis. The syndrome apparently occurs with basophilic adenoma of the pituitary gland and tumors of the adrenal cortex, and rarely of the thymus, or without tumor of any of these organs. The association of a tumor with Cushing's syndrome occurs rarely in the adult male, regularly in the child and commonly

in the adult female. In all cases the basophilic cells show characteristic hyaline changes; it may be, however, that the hyalinization represents a period of over-activity of the basophils as a consequence of inactivation of certain subsidiary ductless glands.

There are a decrease in the estrogens of the blood and an increase in the androgens. Androgens may inhibit the effect of the estrogens on the formation of bone, which may account for the severity of the osteoporosis. The most important factor, however, is thought to be a negative nitrogen balance due to the increased conversion of proteins into sugars.

Osteoporosis is of common occurrence in cases of Cushing's syndrome. Eisenhardt and Thompson found that of 61 patients, ranging in age from 11 to 78 years, 53 had definite osteoporosis, 5 showed questionable changes and 3 had normal bones. In the authors' series of 7 patients, from 19 to 49 years of age, 6 had osteoporosis. The skull was most often involved, but the more striking changes were noted in the ribs and spine. In 1 patient the long bones were involved.

The osteoporosis of the skull, seen in 5 of the 7 patients, was irregular in distribution and occurred most often in the frontal and parietal regions. The areas affected were irregularly triangular or ameboid, with poorly defined margins, or were roughly circular, resembling metastatic carcinoma. In 1 patient the skull showed diffuse coarsely granular mottling. Occasionally only the dorsum sellae was osteoporotic.

The spine revealed uniform osteoporosis, this being found in all segments. The bones were more radiolucent because of a uniform decrease in the number and density of the trabeculae. The osteoporosis may be severe, resulting in compression fractures of the vertebrae, or may be so mild that it is difficult to recognize. It has no specific characteristics.

The ribs show a peculiar change near the costochondral junctions which is almost pathognomonic. It is usually found in the lower ribs and is symmetric as a rule. The ribs are expanded to about twice their normal size for a distance of about 1 inch (2.5 cm.). The area is sharply outlined, as though by a calcified shell. Within this the deposit of calcium is uniform and homogeneous. The affected areas are denser than the surrounding bone, their appearance suggesting callus formation. No fracture line was visible in the present series of cases, although it has been reported. The histologic picture was indistinguishable from callus. Fractures of the vertebral bodies are readily explained as a result of loss of strength due to the osteoporosis. This may also explain the rib fractures, but it is significant that such fractures have not been reported in cases of osteoporosis occurring after the menopause or in association with nutritional disturbances. In Albright's cases of menopausal osteoporosis there was a history of fracture of ribs in only 1 instance.

In 1 case the osteoporosis was extreme, and the humeri and femurs were involved. The more profound changes occurred in the cases of adenoma. The duration of the illness could not be correlated with the severity of the changes observed in the bones. In all the cases there was a tumor of the adrenal cortex—in some a benign adenoma and in others a carcinoma. KENNEDY, Philadelphia.

Society Transactions

AMERICAN ASSOCIATION OF NEUROPATHOLOGISTS

N. W. WINKELMAN, M.D., *President, in the Chair*

Annual Meeting, June 4, 1942

Miliary Aneurysms: Relation of Anomalies of the Circle of Willis to Formation of Aneurysms. DR. HELENA E. RIGGS and DR. C. RUPP, Philadelphia (by invitation).

A study of the circle of Willis in 1,437 consecutive cases demonstrated the presence of aneurysms measuring 0.5 cm. or less in 131 cases (9 per cent). In 28 cases multiple aneurysms were present, as many as 5 being noted in a single case. The absence of any significant increase in the number of these lesions in the older age groups largely eliminates systemic disease, such as arteriosclerosis or hypertension, as a primary etiologic factor. Failure to discover any aneurysms in a group of 102 infants and children under 10 years of age lends confirmation to the theory of Forbus that miliary aneurysms as such are not of congenital origin but that their development is fundamentally related to structural defects in the arterial wall of embryonic origin. The location of the aneurysms in this series of cases strengthens this hypothesis. All these lesions were located in relation to arterial branchings, areas in which, as Forbus has demonstrated, congenital structural defects of the arterial wall are characteristically present.

Site: Arterial Branching	No. of Cases
Anterior cerebral with anterior communicating artery.....	79
Middle cerebral with anterior cerebral artery.....	36
Internal carotid artery with:.....	34
Anterior communicating artery	
Anterior choroidal artery	
Basilar artery with:.....	15
Posterior communicating artery	
Superior cerebellar artery	
Posterior inferior cerebellar artery	
Vertebral artery	
Bifurcation of anterior cerebral artery (second portion)....	6
Bifurcation of posterior cerebral artery.....	2

Forbus suggested that the evolution of aneurysms in such areas is affected largely by mechanical forces and that the high intravascular pressure normally developed at bifurcations, when exerted against the congenitally weak arterial wall in that area, provides the necessary mechanism by which the dilatation is effected. This hypothesis, however, does not account for the failure of aneurysms to develop at all bifurcations at which structural weakness of the wall is present. Further, such a theory is tenable only for the development of aneurysms from areas of structural weakness located at points where the parent stem divides into two branches of equal size. In this study only 26 per cent of the aneurysms occurring at arterial branchings were located at such bifurcations; 74 per cent occurred at the branching of a small artery from the side wall of a parent vessel of greater caliber.

The presence of a high degree of association of aneurysms and anomalies of the circle of Willis ($\chi^2 = 13$) in this series suggests that such structural mal-

formations, by producing local alterations in intravascular dynamics, may provide a mechanical basis for the development of aneurysm in congenitally weak portions of the vascular wall. Analysis of the location of the aneurysms in relation to abnormal formations of the circle of Willis demonstrates that 86 per cent of these lesions lay in fields where anomalies provided a potential source of hydraulic imbalance.

Sarcoma of the Temporal Lobe Associated with Abscess and Invading the Subcutaneous Extracranial Tissues. DR. P. BAILEY, Chicago.

History.—A white woman aged 40 was admitted with the complaint of headache of two months' duration. She had been well until March 1941, when she had a sore throat, from which she recovered promptly. In May 1941 severe generalized headaches began, the pain at first lasting a few days and gradually becoming continuous. She had vomited almost daily for the last three weeks.

Examination on July 14, 1941 showed bilateral papilledema of about 4 D. The visual fields were normal. Roentgenograms of the skull revealed irregularity of structure of the vertex, of questionable pathologic significance. The diagnosis was unlocalized intracranial lesion, probably glioblastoma, with hypertension. A ventriculogram, made on July 15, revealed evidence of a lesion in the right temporal area. A subtemporal decompression was made in this region, and from a cavity thin pink fluid was aspirated; microscopic examination of this fluid revealed no organisms and culture yielded only a few colonies of diphtheroids.

The patient slowly recovered from the operation. The wound gradually became more troublesome, however, and drainage yielded only a small amount of purulent material. The lesion was treated for many weeks with local applications of sulfonamide compounds, and, from July to December 1941, six operations were performed for revision of the abscess cavity, excision of cortex and débridement of an area of osteomyelitis involving the temporal, parietal and frontal bones. The edges of the wound became progressively thickened; in November left hemiparesis followed the débridement, and in December and January the patient received intermittent doses of roentgen rays, amounting to some 1,100 r in all. After the cessation of roentgen therapy, the piling up and thickening of the edges of the wound increased rapidly, and the lesion extended to the vertex of the skull and down the entire right side of the face, involving the face and the right eye in an indurated swelling. Various organisms, including *Staphylococcus aureus*, *Streptococcus haemolyticus*, *Pseudomonas aeruginosa* and *Encapsulatus aerogenes*, were isolated from the wound, which had by now closed to a narrow sinus. The patient became weaker and died April 10, 1942.

Autopsy.—Complete postmortem examination disclosed nothing of importance except for the cerebral lesions. The anterior part of the right temporal lobe of the brain was occupied by a firm, whitish mass, sharply demarcated from the brain tissue and continuous with the indurated subcutaneous tissue of the face and scalp. This tumor was only loosely adherent to the dura mater except around the decompression opening in the skull. Above the tumor, in the dorsal part of the temporal lobe, was the sinus track, with a small collection of pus at its inner extremity. The brain had herniated slightly around the drain. The ventricles were covered by a whitish granular material, which looked like the surface of a cauliflower.

Microscopic Examination.—The intracranial and the extracranial portion of the tumor, as well as the intraventricular nodules, were similar in structure. Broad, streaming bands of elongated cells formed a stroma which divided the neoplastic mass into alveoli. The nuclei of the neoplastic cells were chiefly oval and somewhat vesicular. Mitoses were numerous. Perdrau's method revealed an abundant network of reticulin, lying chiefly in the stroma but often permeating the tumor, in intimate association with the neoplastic cells. There could be

no doubt that the tumor was an alveolar sarcoma of leptomeningeal origin. There was also purulent infection of the brain, meninges and ventricular walls.

Comment.—It is unusual for an intracranial tumor to infiltrate the subcutaneous tissue in this manner. I have never known a glioma to do more than bulge outward through a decompression opening as a well circumscribed mass. Intracranial sarcoma is so rare that I have had no experience with extension into subcutaneous tissues by such a tumor. Is it possible that there was, nevertheless, an abscess and that the neoplasm was caused by the large quantities of a sulfonamide compound used in the wound? Such an explanation would account for the intracranial and the extracranial growth without the assumption that the intracranial tumor spread outward to invade the subcutaneous tissues. That there was a serious infection was proved by the development of osteomyelitis of the skull, but this may have been secondary. It is not likely that irritation from the long-standing infection could have given rise to the neoplasm; such an origin would be without precedent in my experience. Actually, it seems to me impossible to answer these questions.

DISCUSSION

DR. L. H. ZIEGLER, Wauwatosa, Wis.: Several years ago, a boy about 10 years old was referred to me because of headaches, vomiting and evidences of increased intracranial pressure. He had occasional slight fever, but no well defined localizing signs; however, one or two of the cranial nerves were partially palsied. A lumbar puncture, cautiously done, revealed a count of about 50 cells per cubic millimeter of spinal fluid. My associates and I were puzzled to know whether the condition was encephalitis or a neoplasm, but we favored the diagnosis of encephalitis. However, this was in the days before the advent of sulfonamide drugs. The process was progressive, and a subtemporal decompression revealed widespread sarcoma of the meninges. On the patient's death this diagnosis was verified. The sarcoma had in places invaded the brain, especially around blood vessels.

DR. R. B. RICHTER, Chicago: With regard to the experimental angle of the problem, the study by Haerem (*Proc. Soc. Exper. Biol. & Med.* **45**:536 [Nov.] 1940) is of interest. He observed in a tumor-free strain of mice that spindle cell sarcoma developed in 10 per cent of animals given subcutaneous injections of sulfanilamide in lard, while tumor did not appear in any of a large number of control animals given injections of lard alone.

Experimental Studies on Electric Shock Treatment: Intracerebral Vascular Reaction as an Indicator of the Path of the Current. DR. LEO ALEXANDER and DR. H. LOWENBACH, Durham, N. C.

In a previous study by Alexander and Weeks, it was observed that if an electric current of a magnitude sufficient to abolish irritability and conductivity of the nerve fiber was passed through a peripheral nerve, capillary and supra-capillary anemia of the vascular bed established itself in that part of the nerve through which current had been flowing. This anemia lasted until shortly before irritability and conductivity of the nerve returned. More recently, Echlin produced localized cerebral anemia by direct electrical stimulation. While previous experimental work on electric shock, similar to that used in treatment, had tended to show rather diffuse cerebral and meningeal changes, not all of which were of clearcut pathologic significance, the observations by Alexander and Weeks make it appear extremely unlikely that electric current would distribute itself diffusely throughout the brain, but suggested the existence of a fairly clearcut path from one electrode to the other. Therefore, we felt that it was necessary to carry out experiments by which we could outline clearly the characteristic vascular reaction to the electric current.

With doses above the therapeutic level, with respect both to strength and to duration, we produced clearcut capillary and supracapillary anemia of what is morphologically the frontal lobe in the cat (i. e., the frontocruciate region) whenever the electrodes were applied in a way comparable to the usual method of producing electric shock in man—namely, with the current passing from the area in front of one ear to the area in front of the other, through electrodes measuring 100 sq. mm.

This supracapillary and capillary anemia of the frontal region, presumably caused by vasoconstriction as a consequence of the passage of the electric current, lasted up to one and one-half hours. With shock doses comparable to those used in treatment, the anemia (vasoconstriction) one-half hour after the shock was either slight or equivocal, or no change could be recognized at all. It is concluded that no consistent pathologic changes of any significance were caused by shock doses of electric current comparable to those used in treatment and that the fundamental changes caused by the electric shock treatment must be essentially physiologic or physiochemical.

DISCUSSION

DR. L. KALINOWSKY, Brentwood, N. Y.: There are available now several experimental studies in which the current was comparable in intensity and duration to currents used in treatment of human beings. Most of these studies did not reveal any important pathologic change in the brain tissue. The results of Dr. Alexander and Dr. Lowenbach are in full accord with the observations of Cerletti and Bini (*Riv. sper. di freniat.* 64:1, 1940), with the recent studies of Moore and Winkelman and with the work of Barrera and myself. The only investigation in which different results were obtained is that of Alpers and Hughes, who observed numerous hemorrhages in their animals. In this connection, I wish to mention the work of Stender (*München. med. Wchnschr.* 84:1893, 1937), who observed hemorrhages of the same type in animals after metrazol convulsions. He was impressed by the similarity of such hemorrhages to those in cases of concussion and suggested that they might be explained by injury to the head sustained during the violent convulsion. He therefore treated a second series, putting the animals in a padded box during the convulsions. In none of the animals of the second series were hemorrhages seen. This observation may be of possible aid in explanation of the variable results of studies on electric shock convulsions, all the more as Hassin did not see such hemorrhages in the brains of electrocuted criminals, to whom currents of intensities many times those employed in shock treatment were applied.

DR. M. T. MOORE, Philadelphia: Dr. Alexander's presentation has made clear two important facts regarding the effect of an electric current on the smaller vessels of the brain. First, currents of an intensity not in excess of that sufficient to produce a convulsion in the cat, analogous to that observed in human subjects, do not produce rhexis of the intracerebral or the meningeal vessels. Second, when a current of sufficient intensity to produce hemorrhages is used, the hemorrhages occur in the path of the electric current between the electrodes and are not diffusely scattered throughout the brain.

In several recent reports of convulsions experimentally produced by means of electric shock, subarachnoid and intracerebral hemorrhages of rather scattered distribution have been described. It is important, in the light of the evident efficacy of electric shock in the treatment of the affective psychoses, to evaluate these observations. In experiments with convulsions induced in cats, Dr. Winkelman and I have failed to find any evidence of cerebral hemorrhage, or indeed any change of note, when the animals were treated in a manner similar to that used with human beings. Some of the histopathologic changes reported may be attributed to factors other than the passage of the electric current alone. Neumann, Cohn and Katzenelbogen (*Am. J. Psychiat.* 98:671 [March] 1942) observed cerebral changes in a controlled group of 7 cats, of which 3 were permitted to live for several months in the laboratory, 2 were killed shortly after arrival

and 2 died of "sniffles," Examination of the brains of these animals showed pyknosis and edema in 4, toxic encephalopathy in 1, congestion and stasis of the cerebral vessels in 3 and petechial hemorrhages in 2. We, likewise, have observed in control animals similar histopathologic changes, as well as fibrosis of the meninges. Ferraro and Roizin (*J. Neuropath. & Exper. Neurol.* 1:81 [Jan.] 1942), in their work on acute experimental inanition in cats, showed, among other things, vascular changes varying from slight productive alterations to severe involvement, as well as occasional hemorrhages. Prados and Swank (*Vascular and Interstitial Cell Changes in Thiamine-Deficient Animals*, *ARCH. NEUROL. & PSYCHIAT.* 47:626 [April] 1942) demonstrated that in animals with nutritional deficiency, particularly thiamine deprivation, vascular disturbances occurred in the brain, eventuating in petechial hemorrhages. The vascular changes consequent to thiamine deficiency have been stressed by Alexander and others. Alexander indicated that the vulnerability of the wall of the smaller vessels is influenced by such deficiency. In the experimental work of Alpers and Hughes (*Changes in the Brain After Electrically Induced Convulsions in Cats*, *ARCH. NEUROL. & PSYCHIAT.* 47:385 [March] 1942), the first two groups of animals were treated with electric cerebral shock daily except on Sundays. Animals treated in such a manner often show a disinclination to eat, and it is quite possible that these animals suffered from nutritional deprivation. Treatments with the electric current were therefore an added disruptive factor, and it is not inconceivable that the vasculature predisposed to weakness by a vitamin deficiency may have given away, with resulting hemorrhages. It may be noted here that these hemorrhages were fairly widely distributed and did not correspond to the "track" hemorrhages, as illustrated by Dr. Alexander.

DR. N. W. WINKELMAN, Philadelphia: Dr. Alexander and Dr. Lowenbach have shown that with shock doses comparable to those used with human subjects the anemia in the brain one-half hour after the shock was either slight or absent, but with doses above the usual therapeutic level clearcut anemia was produced along the pathway of the current.

I wonder whether the authors studied the eyes of their experimental animals. In human subjects Dr. Moore and I have noted conspicuous congestion of the conjunctiva and sclera almost immediately after the application of the current. There appeared to be no preliminary vasoconstriction.

DR. LEO ALEXANDER, Durham, N. C.: I am grateful to all the discussers for their comments, and I am sure that with their joint efforts some light will be shed on the still unknown basic factors, physiologic, physical and chemical, which are operative in electric shock treatment.

Scarlatinal Encephalomyelitis. DR. N. W. WINKELMAN, Philadelphia.

In the perivenous, demyelinating form of encephalitis many etiologic factors are concerned, but for the most part the disease complicates vaccination and the acute infectious diseases of childhood, such as measles, chickenpox and smallpox, which attack the skin.

Because of the rarity of the encephalomyelitis during scarlet fever, the following case, in which the histopathologic changes conformed to the usual picture of so-called postvaccinal encephalitis, is reported.

In a 9 year old Negro girl signs and symptoms of diffuse involvement of the brain and spinal cord developed on the eighth day of her illness with scarlet fever. She died, with bulbar symptoms, in two days, after a stormy course.

Myelin sheath stains of the cortex, subcortex, basal ganglia, brain stem and spinal cord showed areas of demyelination, which were distributed almost entirely around the veins. Many of the smaller veins contained thrombi in various stages of organization. With cell stains the cortex for the most part revealed architectural disturbance as the result of mild loss of cells, increase in the macroglia and microglia and perivenous cuffing, made up of a narrow zone of hematogenous

elements (lymphocytes and plasma cells), surrounded at times by a wide band of microglia cells and phagocytes. The subarachnoid space was invaded only secondarily by a few inflammatory and phagocytic elements.

The changes in the subcortex were highly developed. There the perivenous involvement reached a maximum, with cuffing of the vessels by a few lymphocytes and plasma cells, intermingled with many phagocytes and microglia cells, the infiltration reaching far out into the tissues, without sharp delimitation. A generalized macroglial increase was present.

The changes in the brain stem were of a similar nature but of somewhat less pronounced degree. The perivascular accumulations showed fewer hematogenous cells, with microglia cells and phagocytes streaming out into the parenchymatous substance. The ganglion cells were spared in great measure, but they presented acute changes of various kinds.

The spinal cord showed changes similar to those of the rest of the central nervous system. Both the gray and the white matter were involved. Severe perivenous demyelination and cellular reaction, resembling the changes in the brain stem, were noted. The motor cells of the ventral horn were fewer, although normal cells could be seen. The membranes, especially those in relation to the anterior fissure, showed an inflammatory reaction. Marginal gliosis of severe degree bordered the anterior fissure but was less pronounced around the rest of the cord. The spinal ganglia were completely surrounded by hematogenous cells, together with some phagocytic elements. The ganglia themselves were not directly invaded by these elements.

The cerebellum showed changes of the same type as those noted in the rest of the central nervous system. Here, also, the white matter was chiefly affected.

This study, centered around a single case report, disclosed three important facts. 1. Unlike other exanthems, scarlet fever is rarely complicated by encephalomyelitis of the perivenous type. 2. The conclusion of Ferraro and Scheffer that the perivenous type of encephalomyelitis is not an inflammatory process in the strict sense of neuropathologic nomenclature, and that it should be termed an encephalopathy, is probably correct. 3. Perivenous encephalomyelitis usually occurs with acute exanthemas due to virus infection. Scarlatina, a streptococcal infection, is the exception to the rule. The histopathologic picture, however, conforms to that of postvaccinal encephalomyelitis and does not resemble the primary virus encephalitides, as exemplified by rabies, poliomyelitis and St. Louis encephalitis.

DISCUSSION

DR. I. J. SANDS, Brooklyn: For the past decade I have followed the neurologic material at the Kingston Avenue Hospital for Contagious Diseases. The cases are drawn from a population of approximately 3,000,000. Seldom, if ever, does true encephalitis complicate scarlet fever. A scarlatinal rash in Negroes is sometimes difficult to recognize, and frequently other types of rashes may be mistaken for the eruption of scarlet fever. I have known clinicians of long experience to disagree on the diagnosis of such a rash. Without intending to disparage the diagnostic skill of those in charge of this case, I reserve the right to question the original clinical diagnosis. The patient obviously had encephalomyelitis, but the cause was unknown.

DR. ARTHUR WEIL, Chicago: I am not quite as skeptical as Dr. Sands with respect to the clinical diagnosis in this case, but I agree with Dr. Winkelman that the histopathologic picture which he demonstrated is unusual for a case of encephalitis following scarlet fever. From the few cases reported in the literature and my own limited experience, it appears that metastatic, emboli-disseminated encephalitis may occur after infections of the kidneys, lungs and other organs. The condition may be accompanied by multiple small hemorrhages or by purpura of the brain. I cannot agree with Dr. Winkelman that the lesions in his preparations resembled those of encephalitis following measles. In the latter condition the gray matter is usually spared, while in the present case there was a massive

inflammatory reaction in both the gray and the white matter. Furthermore, with measles one usually does not see such severe meningitis and such pronounced perivascular lymphocytic infiltration; the perivascular gliosis and necrosis are more prominent in measles.

The term demyelination is rather loosely used in present day literature; frequently the author does not state whether there is disappearance of the myelin sheaths alone or whether the paling in his myelin-stained preparations indicates also a breaking down of axis-cylinders, a complete necrosis of the axon, as it may be seen in the perivascular foci of measles encephalitis in adequately silver-impregnated sections.

DR. N. W. WINKELMAN, Philadelphia: I agree thoroughly with Dr. Sands with respect to the difficulties of diagnosis of scarlet fever in a Negro child. In this case, however, the patient was examined at a municipal hospital where Negroes are treated in large numbers. The staff members were unanimous in their conclusion that the patient was suffering from scarlet fever and that the neurologic manifestations were the result of that condition.

Dr. Weil is correct in his statement that the complication of encephalitis in the course of scarlet fever is extremely rare; for that reason alone this case was made the subject of a special report. I am in accord with Dr. Weil in regard to the greater involvement of the white matter, but I do not entirely agree that the gray matter is usually spared. In most cases of measles encephalitis or of postvaccinal encephalitis there is some involvement of both the cortex and the subcortex. Globus (*Infections of the Central Nervous System, A. Research Nerv. & Ment. Dis., Proc.* [1931] 12:33, 1932) stated that in the postvaccinal type of encephalitis "the inflammatory changes . . . show no preference for the white or gray matter."

I agree that the term demyelination is used loosely by most authors. In my case there were actual perivascular necroses to account for the loss of myelin sheaths around the veins.

New Staining Method for Demonstration of *Debaryomyces Neoformans* (*Torula Histolytica*), *Blastomyces Hominis*, *Coccidioides Immitis* and *Histoplasma Capsulatum* in Histologic Preparations. DR. J. W. KERNOHAN, Rochester, Minn.

This study was undertaken because of the difficulty of demonstrating *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and certain other fungi in histologic preparations. Cresyl violet stains the capsules of these organisms pale sky blue and the contents of the capsule frequently rose or pink.

With Meyer's mucicarmine, *Debaryomyces neoformans* stains scarlet; the capsules of *Blastomyces* and *Coccidioides immitis* and certain other fungi are red, and the contents take a variable color but frequently do not stain.

With Best's carmine, the capsules and organisms stain a deeper hue, but since the background is also darker, the contrast is little, if any, improved.

With silver stains, these organisms are outlined sharply and are distinguished readily. I have counterstained the silver preparations with the carmine stain recommended by Best for the demonstration of glycogen. This combination of methods is superior to any I have encountered. The organisms (*Debaryomyces*, *Blastomyces*, *Coccidioides*, etc.) all stain scarlet and are sharply outlined with the silver. This combined stain also eliminates the pink or reddish background which is so objectionable with the Best carmine stain alone. The latter is apparently not specific for glycogen, but demonstrates in a characteristic manner amebas, certain yeasts and fungi, and so forth. In a recent case of infection of the heart valve with *Histoplasma capsulatum* the combined stain demonstrated the organisms clearly and differentiated them from the surrounding tissue. The cytoplasm of the organisms was scarlet and contained small granules of material impregnated with the silver. Furthermore, the organisms varied in size, from the small variety usually noted to very large forms. The latter resembled closely

large yeastlike bodics, and a few contained numerous small forms simulating endospores. On the other hand, some of the organisms of intermediate size were forming buds. This variation in size and form of *H. capsulatum* should be investigated by a competent and experienced mycologist.

DISCUSSION

DR. LEO ALEXANDER, Durham, N. C.: All who have struggled with the difficult problem of staining these organisms satisfactorily will be grateful to Dr. Kernohan for his important contribution.

DR. PERCIVAL BAILEY, Chicago: Watts, in a paper on *Torula* infection (*Am. J. Path.* 8:167 [March] 1932) published from my clinic, showed that Masson's technic for mucicarmine is an excellent stain for yeast. The organisms stain red against a clear yellow background (mctanil yellow).

DR. WALTER FREEMAN, Washington, D. C.: Dr. Kernohan has shown some exceptionally beautiful preparations demonstrating these parasitic invaders in the meninges of the central nervous system. It is admitted that ordinary hematoxylin and eosin preparations are unsatisfactory, and there is such a variation in the staining reaction of the organisms to thionine and so little of the tissue visible with the Gram stain that this method has its place. Personally, I have used the Perdrau silver impregnation method with rather satisfactory results; the organism shows up prominently.

Histogenesis of Cerebral Arteriosclerosis. DR. G. EROS, Orangeburg, N. Y., and DR. A. FERRARO, New York.

Our report deals especially with the histogenesis of the vascular changes in over 50 brains for which a clinical diagnosis of cerebral arteriosclerosis had been made. On the basis of our studies, we feel that the primary, and most important, changes take place in the elastic tissue of the blood vessels, especially in the so-called internal elastic membrane. All the other degenerative changes, such as fatty and mucoid degeneration, calcification, fibrous proliferation and hyalinization, are only secondary to the changes in the elastic tissue.

Two main types of degenerative changes can be distinguished: (1) the hyperplastic and (2) the hypoplastic.

In the hyperplastic degenerative type there is a pronounced tendency to proliferation of the elastic tissue in the larger, as well as in the smaller, arteries of the brain. The internal elastic membrane shows reduplication and multiplication even in the early stages. This hyperplasia of the elastic tissue is the primary factor and is at times accompanied by, or generally followed by, degenerative changes and fibrous proliferation of the intima.

In the first stage the newly formed elastic fibers and lamellas are darkly stained and sharply outlined, and the degenerative changes are not pronounced. Later the deposition of fatty substances is gradually increased and is accompanied by fibrous proliferation of the intima. In the more advanced stages the elastic lamellas and fibers become paler, their outlines lose definition and the deposition of fatty substances is particularly pronounced in the deeper layers of the intima. In advanced stages the proliferated elastic fibers and lamellas disappear, being partially or totally replaced by fibrous connective tissue. In these late stages there are usually conspicuous fatty and mucoid changes, hyaline degeneration and, eventually, deposition of calcium in the intima. The lumen of the arteries becomes narrower, owing to proliferation of the intima. As the pathologic process progresses, these proliferative and degenerative alterations gradually involve the other layers of the artery, especially the media.

In the hypoplastic degenerative type there is little, or no, tendency to proliferation of the elastic tissue. The elastic membrane is pale and indistinct in outline, even in the earliest stages of arteriosclerosis. Reduplication or multiplication of the layers of the elastic membrane is not evident. In later stages the elastic membrane is swollen, pale, loose and folded. In many arteries exhibiting this type of degeneration the internal elastic membrane seems to have undergone thickening, which closer study reveals to be pseudothickening, the result of

swelling of the degenerated elastic membrane. The swollen membrane is lacking in elastic substance. Fat stains may show fatty degeneration of the intima in the very early stages. These degenerative changes in the elastica in some arteries may be accompanied by moderate fibrous proliferation of the intima, but in many of the arteries no fibrous thickening of the intima or appreciable diminution of the lumen of the arteries is noticeable. On the contrary, the lumen is usually wider than normal, and the walls of blood vessels show deformities and indentations, presumably related to loss of elasticity. In more advanced stages the degenerative changes may gradually involve the other layers, with subsequent fibrosis, fatty degeneration or hyalinization of the entire wall. However, in these advanced stages some of the degenerated arteries remain wide open and do not disclose appreciable diminution of their lumen.

While this distinction between the hyperplastic and the hypoplastic type of cerebral arteriosclerosis holds true for the intracerebral blood vessels, the large arteries of the circle of Willis are likely to show a less evident difference because of their greater tendency to major proliferation of the elastic tissue and degenerative changes in the entire wall. Neither the hypoplastic nor the hyperplastic variety seems to be related to advanced age, inasmuch as the degeneration may appear in comparatively young persons.

Constitutional factors may play an important part in determining the type of reaction of the blood vessels to all sorts of pathogenic agents. This contention is in support of the statement that arteriosclerosis is not a disease of advanced age only but is determined by the constitutional makeup of the vascular system.

In the hypoplastic degenerative type of arteriosclerosis diffuse vascular disturbances may develop, which may lead to diffuse parenchymatous changes rather than to circumscribed softenings. In the hyperplastic degenerative type the intimal proliferation and the diminution of the lumen of the arteries lead, rather, to various types of softenings and accompanying focal symptoms. In the hypoplastic type hemorrhages occur even in the early stages and appear more often than in the hyperplastic type. We have never encountered hemorrhages accompanying the hyperplastic type of vascular change except in the later stages, when severe degeneration takes place.

DISCUSSION

DR. C. E. BENDA, Wrentham, Mass.: Arteriosclerosis is a well defined clinical and pathologic entity, and general pathologists have been concerned to a great extent with the problem of arteriosclerosis of the arteries of the body. Of the pictures which Dr. Eros demonstrated, only a few showed what one would call arteriosclerosis of the cerebral vessels. The other slides presented various types of hypertrophic fibrosis of the arteries or atrophic and degenerative changes.

One might study the condition of the cerebral arteries in cases in which the general pathologist has recognized pronounced arteriosclerosis in the vessels of the body organs. Dr. Eros and Dr. Ferraro noted little arteriosclerosis in the brain in their investigation. I doubt, however, whether the condition of the cerebral arteries was their primary concern, for Dr. Eros stated that they noted no relation between the age of the patient and the so-called arteriosclerotic changes in the brain. Examination of the cerebral vessels in cases of severe arteriosclerosis of the coronary and other arteries shows frequently little arteriosclerosis of the vessels of the brain; I was especially impressed in studies on paralysis agitans by the frequency with which the vessels in the brain were free from arteriosclerosis when the pathologist had reported advanced arteriosclerosis in the body organs. My experience is in accord with that of several other investigators.

On the other hand, I fear that the application of the term arteriosclerosis, which is well established in general pathology, to the changes in the cerebral vessels which these authors observed will lead to great confusion. Hypertrophy of the intima is seen in many conditions, especially chronic infectious diseases; if one studies the arteries leading to a tuberculous organ, one usually sees proliferation of the intima in that area. In most diseases of the brain the arteries react either

with hypertrophic or with degenerative changes, and in the brains of children 2 or 3 years of age I have seen changes similar to those the authors presented. In hardly a single case with pronounced pathologic changes in the brain did careful study of the cerebral arteries not discover considerable alteration of the vascular walls. If one is going to call all such changes arteriosclerosis, one will be confronted with a huge amount of arteriosclerotic conditions of the brain of various types. The term arteriosclerosis should be reserved for those conditions in which the vessels undergo primary degenerative metamorphosis, with fatty degeneration of the intima and media. Arteriosclerosis of the vessels of the brain does occur, although it is rare, and a study of conditions under which arteriosclerosis of the cerebral vessels is to be found would be of special interest.

DR. LEO ALEXANDER, Durham, N. C.: I am inclined to agree that the subtle changes which the authors described belong in the wider field of the lesions one is justified in calling arteriosclerosis.

DR. N. W. WINKELMAN, Philadelphia: I have always believed that arteriosclerosis is a clinical rather than a pathologic term. Some years ago Dr. Patten and I studied the blood vessels in a large group of patients over 50 years of age. We divided the changes in the blood vessels into three main types: first, the atheromatous change, which corresponds to the authors' hypertrophic degenerative type; second, arteriofibrosis, which corresponds to their atrophic degenerative type, and, third, hyalinization of the media, which occurs mainly in the medium-sized arteries, rather than in the large basal vessels.

We felt that our classification was important because it gave us some idea of the clinical picture. We found that patients with the arteriofibrotic type live to be older than did those with changes of the other two types. Many patients with the arteriofibrotic form showed no evidence of the usual senile mental changes that are so prevalent with the atheromatous type. With the latter type there was a tendency to hypertension, and the patients did not live as long as those with arteriofibrosis. Frequently the atheromatous type was associated with hyalinization of the medium blood vessels. It was among patients with this form of degeneration that the most severe hypertension occurred, with relatively short duration of life, frequently not beyond 50, and prominent mental and neurologic disturbances.

DR. I. M. SCHEINKER, Cincinnati: I do not agree with Dr. Benda's criticism or with his statement that the slides which were presented did not demonstrate arteriosclerotic changes. I believe that the preparations illustrate the most characteristic feature of the early stage of cerebral arteriosclerosis. As a matter of fact, degeneration of the media associated with circumscribed plaque formation, the criterion required by Dr. Benda, is not the characteristic change in cerebral arteriosclerosis. The seat of degeneration of the vessel wall in the vessels of the brain seems to differ from that in the vessels of other organs. Involvement of the media by plaque formation is exceptional in cases of cerebral arteriosclerosis, and therefore it cannot be considered characteristic. I agree heartily with the authors that the changes demonstrated in the elastic membrane and the proliferation of the intima are the most characteristic pathologic features of the early stage of cerebral arteriosclerosis.

DR. G. EROS, Orangeburg, N. Y.: According to present knowledge, arteriosclerotic changes in the cerebral vessels are represented by a combination of several characteristic degenerative and productive changes in the vessel walls. Arteriosclerosis is a well defined clinical and pathologic entity, as Dr. Benda states. Hyperplasia of the intima of the cerebral blood vessels other than the arteriosclerotic type, as well as deposits of simple fat in the intima and media, can be mistaken for cerebral arteriosclerosis only by one not familiar with the clinical, macroscopic and histologic manifestations of cerebral arteriosclerosis. We did not say that arteriosclerosis was represented in our material only by simple intimal hyperplasia of some cerebral arteries. On the contrary, we showed in our photographs the gradual development of the characteristic severe arteriosclerotic change from its beginning in the elastic tissue.

As our present contribution to the problem of cerebral arteriosclerosis is in the field of histogenesis, we have illustrated the first stages of arteriosclerosis, with special emphasis on the beginning and the advanced changes in the elastica, which, in our opinion, constitute the primary factor in the development of cerebral arteriosclerosis. For this reason, we have shown sections stained for elastic tissue which demonstrate that these changes in the elastica are generally uncomplicated at the beginning. Later, they are followed by other degenerative and productive changes in the arterial wall characteristic of arteriosclerosis. We were able to follow these changes from the early to the far advanced stages because arteriosclerotic changes are not the same everywhere in the same brain. In some regions of the brain such alterations may be severe, while in others they are only moderate, slight or just beginning. I wish to emphasize again that the cerebral arteries in all our cases showed various degrees of arteriosclerotic change, from very early, mild alterations to far advanced ones, accompanied by pronounced parenchymatous changes and by softenings of or hemorrhages in the brain substance. All our cases were clinically, as well as pathologically, instances of pronounced cerebral arteriosclerosis, with prominent mental or neurologic manifestations.

With regard to age, neither of the types described by us seems to be restricted to advanced age, and arteriosclerosis of both types can be observed in relatively young persons. We do not believe, however, that the changes in the blood vessels demonstrated by us could be observed in the brain of a 2 to 3 year old child. The terms, such as "marked alteration of the blood vessels," which Dr. Benda used in his comment on the changes in the blood vessels which he has observed in the brains of children, do not give a clear idea of his meaning.

Degenerative or productive changes in the elastica of the cerebral blood vessels, with splitting of the elastic membrane, can be detected in conditions other than arteriosclerosis, even in children. But these lesions cannot be mistaken for those of arteriosclerosis, in spite of the fact that the degenerative and proliferative changes in the elastica are important factors in arteriosclerosis as well.

Though it is true that the severity of cerebral arteriosclerosis is not always related to the severity of the arteriosclerotic changes in other regions and organs in the same person, we should not say that cerebral arteriosclerosis is a rare disease. On the contrary, because of its frequency, especially in older persons, it represents an important problem for the psychiatrist and neurologist.

DR. A. FERRARO, New York: I, too, wish to emphasize that our presentation was intended primarily to illustrate the early stages of cerebral arteriosclerosis. We were not interested in demonstrating the end result of such a condition, in which productive and degenerative changes may lead to partial or total occlusion of the blood vessels; therefore, Dr. Eros' slides were intended to overemphasize our contention that the primary damage takes place in the elastic tissue. We could have shown dozens of slides illustrating the terminal phase of hypertrophic degenerative arteriosclerosis. Our conception of a primary pathologic process in the elastic tissue led us to distinguish two types of vascular reaction: one, in which primary hyperplasia of the elastic tissue dominates, and the other, in which primary hypoplasia and inadequacy of the elastic tissue constitute the initial vascular pathologic process.

On the other hand, all the brains in our series disclosed macroscopic indications of cerebral arteriosclerosis in the generally accepted meaning of the term, evidence confirming the clinical diagnosis of psychosis with cerebral arteriosclerosis. Our studies dealt principally with early stages of the vascular pathologic process leading to the typical macroscopic feature of arteriosclerosis.

This paper will appear in a future issue of the *Journal of Neuropathology and Experimental Neurology*.

Gliomatous Tumors in the Nasal Region. DR. EDWARD W. DAVIS, Chicago.

Glioma is rarely encountered in the nasal region but is interesting from the standpoint of tumor genesis. The case of a child 6 months old who had such a

glioma at birth, anterior to the nasal bones, is presented. The tumor was composed predominantly of glial tissue with abundant blood vessels. Similar cases from the literature are briefly noted, and theories of the origin of the glioma are discussed.

This paper was published in the July 1942 issue of the *Journal of Neuro-pathology and Experimental Neurology*, page 312.

Vascularization of Cerebral Neoplasms Studied with the Fuchsin Staining Method of Eros. DR. S. ARIETI, Brentwood, N. Y.

This paper is a study by the fuchsin staining method (Eros) of the vascular pattern and morphologic characteristics of blood vessels in various types of cerebral neoplasms. Both the distribution and the morphologic characteristics of the vessels are considered. The vascularization of medulloepithelioma, medulloblastoma, spongioblastoma multiforme, unipolar and bipolar spongioblastoma, astrocytoma, oligodendroglioma and mixed gliomas was studied.

In the medulloepithelioma the angioarchitecture consists of a fine network of capillaries, very thin, and particularly numerous in the periphery of nodular nests of cells. In 2 medulloblastomas a fine, irregular web of capillaries and precapillaries was the chief vascular feature. The vascular pattern of the spongioblastoma multiforme consists of a central area almost deprived of blood vessels and of a peripheral part provided with numerous blood channels, varying from large sinusoids to channels of precapillary size, irregularly arranged, with beadlike deformities, looping and irregular branching.

The idea is advanced that from their vascularization it is possible to recognize a progressive maturity of the gliomas in agreement with the classification of Bailey and Cushing.

The importance of the abnormality of the vascular pattern in the mechanism of growth of the intracranial tumors and in their possible distant effects is stressed.

Fibroblastic meningioma exhibits large blood vessels entering the capsule. In addition, many minor vessels and capillaries are noted in the capsule and in the connective tissue septums dividing the tumor into irregular nodes. These blood vessels provide vascularization to the inner parts of the tumor. Minor vessels extend into the peripheral parts, and even to the center, of the cellular nodules. This distribution of the vessels, which seems to provide a fairly adequate supply of blood to the tumor, explains the infrequency of necrosis and cyst formation in fibroblastic meningioma. In angioblastic meningioma arborescent structures are the commonest feature. In the fibroblastic meningioma the vascularization is mostly capsular; in angioblastic meningioma it is mostly intracapsular.

Knowledge of the vascular pattern of these neoplasms may be useful not only from a morphologic point of view but in diagnostic arteriographic or histologic procedures. It may also contribute to a better understanding of the different mechanisms of growth in the various types of glioma. It is possible to recognize in several types of tumors a characteristic abnormal vascular pattern which undergoes progressive or regressive changes because of such factors as the distribution of its own elements, the compression exercised by them and the endarteritic processes. On the other hand, these changes in the vascular pattern may cause other alterations in the cellular components of the tumor. A vicious circle thus forms, which may lead to decay and necrosis of a great part of the neoplasm.

Furthermore, it must be stressed that the vascular changes mentioned and the resulting imbalance in hydrodynamics not only act within the tumor but often have far reaching effects.

Paraneoplastic engorgement of the pial vessels may result from transmission of the blood pressure from the tumor to other parts which are more susceptible to expansion than are the vessels in the relatively free subarachnoid space. However, one should bear in mind that in the normal tissue surrounding the tumor the blood vessels are often compressed by the contiguous neoplasm. As a matter of fact, fuchsin stains fail to show any structure in some parts of the paraneoplastic area. It is therefore possible that in many cases the dilatation of the meningeal blood vessels is related to the stagnation of the blood, which cannot reach non-

neoplastic regions that are compressed by the tumor. These considerations stress the importance of distant vascular alterations. Some of the neighborhood symptoms observed in cerebral tumors might be ascribed to them.

DISCUSSION

DR. L. ALEXANDER, Durham, N. C.: The author has completely confirmed the observation of Dr. Sahs and myself in regard to this interesting problem.

DR. A. L. SAHS, Iowa City: Several years ago Dr. Alexander and I (Sahs, A. L., and Alexander, L.: Vascular Pattern of Certain Intracranial Neoplasms: Studies with the Benzidine Stain, *ARCH. NEUROL. & PSYCHIAT.* **42**:44 [July] 1939) studied the vascular pattern of a group of intracranial neoplasms. I am gratified to know that our observations are confirmed by another staining method. The fuchsin stain has the advantage of being applicable to material which has been fixed for variable periods, while the benzidine stain must be used on relatively fresh material. With respect to the gliomas, one can say in general that the relative bizarreness and irregularity of the vascular pattern are a reliable index of the malignancy of the tumor.

DR. PERCIVAL BAILEY, Chicago: Neither the Eros nor the Pickworth method demonstrates the entire vascular bed, since they are methods for staining erythrocytes.

DR. N. W. WINKELMAN, Philadelphia: Has Dr. Arieti had the opportunity of studying by this method tumors which had been irradiated? I ask because I am interested in the action of radiation on tumors in general. Do the rays act directly on the tumor cells or through the medium of the blood vessels, and therefore the blood supply?

DR. S. ARIETI, New York: In answer to Dr. Winkelman's question, I did not have the opportunity of studying the vascularization of brain tumors which had been irradiated.

In answer to Dr. Bailey's comment, even though the Pickworth and Eros methods stain erythrocytes, comparative studies with vascular injections show the satisfactory visualization of the capillaries with the Eros method. On the other hand, fuchsin, which is used in the Eros method for less differentiated sections, stains the walls of the blood vessels also.

This paper was published in the October 1942 issue of the *Journal of Neuro-pathology and Experimental Medicine*, page 375.

Myoclonus Epilepsy: Clinicopathologic Report of a Case. DR. L. ROIZIN and DR. A. FERRARO, New York.

A girl aged 16 years first had convulsions at the age of 14 years, after an appendectomy. The character of the involuntary movements which were noticed in the course of unconsciousness, and in its absence, pointed to a clinical diagnosis of myoclonus epilepsy. The patient's brother died of the same condition, and a sister was admitted to the Craig Colony for Epileptics at the age of 15 years and died a year later of a streptococcic infection. Thus, the familial trend of the condition is established.

Histopathologic study of the brain revealed a large number of nerve cells with characteristic cellular inclusions, resembling the bodies described by Lafora under the heading of "amyloid bodies." Such inclusions were present in most of the cortical areas but were more numerous in the dentate nucleus and in the substantia nigra, the latter having practically lost its normal pigmentation. Several types of degenerative changes in the nerve cells were also observed in various areas.

Histochemical studies were carried out in order to establish the chemical nature and histogenesis of these cellular inclusions. The cellular inclusions usually gave a positive reaction for amyloid. However, in certain limited areas or in individual nerve cells the reaction was either completely negative or only partially positive. In other cells the inclusions gave only a more or less intensely positive reaction for hyalin, fibrinoid or carbohydrate.

Frequently the same cellular inclusion reacts positively to tests for various substances, such as fibrin or hyalin, with or without amyloid. This combination of various substances seems to have its equivalent in the appearance of the individual inclusion. Each concentric stratum of the inclusion may take a different reaction. Each layer gives only one reaction, the whole stratum being uniformly positive for one or another reaction.

In view of the complex nature of the amyloid substance and of the still debated phase of its development, one may speculate on the relation of the variation in histochemical reactions to the complex chemical structure of the body and the correspondence of the different chemical reactions to different stages of the development or metabolism of the amyloid substance.

This view seems to be supported, also, by the positive reaction of some of the inclusions to methods meant to detect carbohydrate and protein substances, which may constitute a link in the formation of amyloid.

In view of these morphologic and histochemical considerations, we believe that it is in the interest of precision to avoid the term amyloid bodies, and we suggest instead "heteromorphic inclusions," i. e., bodies differing in morphologic appearance or structure at different stages of formation.

An interesting feature of this case was the presence in the frontal lobes of a large area of telangiectasis. This telangiectasias, though more pronounced in the frontal lobe, affected scattered blood vessels in other areas, which appear dilated.

DISCUSSION

DR. G. B. HASSIN, Chicago: The cell inclusions were first described not by Lafora but by Bevan-Lewis in an epileptic idiot, in the second volume of *Brain* (1879). These structures are so commonly myoclonus epilepsy that one is tempted to identify them associated with myoclonic epileptiform contractions. I have seen them in vast numbers in a case of amaurotic family idiocy, the late infantile type of Jansky and Bielschowsky, of which only 6 instances have been recorded. The patient exhibited continuous clonic contractions of the eyelids and the muscles of the lower extremities, which did not subside even during sleep—veritable *épilepsie continua*. I consider the case one of myoclonus epilepsy in view of the sole presence of clonic muscular contractions. The inclusions were in the form of amyloid bodies, which stained brilliant green with toluidine blue and brown with the silver method of Bielschowsky. In fact, they could be stained by any method except that for amyloid. The inclusions were lodged within the cytoplasm of the nerve cells, and the nucleus was not involved. These bodies indicate a metabolic disturbance, as was assumed by Lafora, and may be considered to be what Alzheimer called *Abbau*.

DR. WALTER FREEMAN, Washington, D. C.: Relatively few of this kind have been reported, none that I know of in which so many methods have been employed, with such a revelation concerning the structure of these inclusion bodies and with presentation of so excellent an argument with respect to their nature. The very fact that these bodies have a concentric arrangement seems to denote a process of hysteresis, similar to that observed in the precipitation of insoluble salts in gels; yet the lack of any crystalline structure, as observed under the microscope, indicates that these intracellular bodies are highly complicated chemical compounds, certainly more than simple salts of iron, calcium and phosphorus. The exact nature of these inclusion bodies is by no means clear. There is no reason to believe that they are virus inclusions, nor do they seem to be associated with actual degeneration of the cell, since the nuclear membrane and nucleolus, although displaced, appear relatively normal. These bodies must, however, in some way interfere with the proper function of the nerve cells, in view of the obvious deteriorating nature of the disease and the peculiar motor manifestations.

Has Dr. Roizin any explanation for the fissured arrangement sometimes seen in these bodies? Has he observed them, as I have, deposited wholesale in the substantia nigra? Many years ago, at St. Elizabeths Hospital, Lafora described these inclusions, and I had the opportunity of comparing the sections in his case

with those in a case encountered in my own experience. The changes are so characteristic that the diagnosis is easily established.

DR. L. ROZIN, New York: With respect to the spheroid bodies which Bevan-Lewis described within the nerve cells of the cortex in a case of "epileptic idiocy," one wonders whether these inclusions can be considered analogous to or identical with the amyloid bodies of Lafora, for in his description Bevan-Lewis expressed the opinion that they were granules, closely packed in the nerve cell from its apex to its basal extremity. In the absence of any detailed morphologic and chemical description, it is difficult to establish the analogy between these granules and the so-called amyloid bodies of Lafora.

I have had the opportunity of studying some of the cellular inclusions associated with amaurotic idiocy, which in my estimation did not resemble the so-called amyloid bodies. They consisted rather of granules of various sizes, which stained particularly well with safranin and resembled the so-called safranophil bodies described by Didé and Bogaert. It is of interest, however, to note that Dr. Hassin has observed amyloid bodies in nerve cells in cases of the late infantile (Jansky-Bielschowsky) form of amaurotic idiocy. The case of amaurotic idiocy to which I referred was one of the Vogt-Spielmeyer type.

In answer to Dr. Freeman's inquiry, at the present stage of the investigation I have no explanation for the fissured arrangement which is sometimes seen in these bodies. In our case we observed a considerable amount of cellular inclusions in the substantia nigra, which was one of the areas most severely involved.

This paper was published in full in the July 1942 issue of the *Journal of Neuropathology and Experimental Neurology*, page 297.

Changes in the Eyes in Amaurotic Family Idiocy (Infantile Type of Tay-Sachs Disease): Histopathologic Observations in a Case. DR. G. B. HASSIN, Chicago.

The eyes, together with the brain and spinal cord, in a typical case of amaurotic family idiocy, were removed sixteen hours after death.

The following conclusions are drawn from the study of this material:

1. The changes in the retina and optic nerves in patients suffering from amaurotic family idiocy are analogous to the changes in the central nervous system in general.

2. The perioptic spaces exhibit the presence of elements similar to those seen in the subarachnoid spaces of the brain and spinal cord.

3. The hyperplasia of the pial septums in the optic nerves is analogous to that of the pia-arachnoid and is a reaction of the latter to the presence of abnormal products of activity of the ganglion cells discharged there by way of the perioptic spaces.

4. Status spongiosus—a manifestation of severe destruction of nerve tissue—is a striking feature in the changes in the optic nerve associated with amaurotic family idiocy.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *President, in the Chair*

Regular Meeting, Oct. 9, 1942

Value of Formal Psychiatric Examinations in the Criminal Court. DR. S. HARVARD KAUFMAN (by invitation).

The history of the role of the psychiatrist in the criminal court is reviewed, with consideration of the various shortcomings of the relation between law and psychiatry. The wider use of psychiatry and sociology in the juvenile court is mentioned as an example of the future role of the criminal psychiatrist. The need

of psychiatric examination of convicted criminals is indicated by the fact that many persons with psychopathic problems are, unfortunately, committed to the penitentiary and later have to be transferred to psychiatric institutions. The formation of an experimental court clinic is described, and 4 case histories are given to demonstrate the procedure employed in this clinic. Forty-two, or 29 per cent, of 146 persons sentenced in the court during the time this clinic was functioning were seen by the psychiatrist.

Various psychiatric problems are discussed. The value and limitations of psychiatric opinion in their solution are mentioned, and the hope is expressed that, in spite of the comparative inflexibility of the criminal law, a greater tendency toward the use of orthopenology and correctional therapy with the aid of psychiatric examinations in the court may come about.

Masochistic Motives in Criminal Behavior. DR. PHILIP Q. ROCHE.

Consideration is directed to the problem of self-thwarting trends and the "need of punishment" as often discerned in the behavior of criminals, especially in those who are parole violators and recidivists. Such self-abnegating trends and the attainment of punishment are reflections of "moral masochism," and they are more evident in the criminal character than is ordinarily suspected. Several aspects of the criminal behavior pattern are discussed. 1. Basically the criminal behavior is infantile and has its prototype in the asocial drives of the child. 2. The criminal act has a symptomatic kinship with psychoneurotic conflict, and it often represents a resolution of anxiety. 3. Humiliation, physical abuse and ostracism obtain for the criminal a masochistic gain and satisfaction similar to that which the psychoneurotic person attains in functional symptoms. 4. Punishment, like symptoms, seldom if ever achieves a desirable modification of the character, but tends rather to fix the criminal in his neurotic dilemma and to prevent him from gaining access to his inner conflict and self-thwarting drives. The author points out that the criminal is rarely able to give a logical explanation for his criminal act, as if he were as helpless as the psychoneurotic patient, who is unable to explain his symptoms. It is emphasized that the aim of the masochist is not suffering per se but the "forgetting of one's self," the obliterating of one's self in the effort to overcome the conflict engendered by one's helplessness, powerlessness and insignificance.

This paper was published in full in the *Journal of Criminal Psychopathology* (4:431-444 [Jan.] 1943).

DISCUSSION ON PAPERS BY DR. ROCHE AND DR. KAUFMAN

DR. HUGO STAUB, New York: For many years I have been interested in the relationship of the psychiatrist to the court, and I am pleased that much progress toward utilization of the psychiatrist in court proceedings has been made during the past fifty years. There has always been mild antagonism between the officers of the court and the psychiatrists, because the two groups speak different languages. The court is interested primarily in punishing the criminal in order to prevent future crimes, while the psychiatrist is interested in the criminal as a clinical problem. This has led to considerable disagreement, which is most noticeable when the psychiatrist is called on to discuss the criminal's responsibility.

The increased interest in motives, drives and emotional conflicts that has arisen from Freud's pioneer work in dynamic psychology has been of considerable value in clarifying the position of the psychiatrist.

I believe that much criminal behavior arises out of immature emotional reactions. The prison environment can be of little benefit in the treatment of such immaturity; as a matter of fact, it tends to increase the immaturity and dependence of the criminal by providing him with many of his basic physical needs. It appears, then, that the immature criminal should be placed in an environment in which he can grow up emotionally, and that in this respect the prison is quite useless.

DR. DAVID ABRAHAMSEN, Kew Gardens, N. Y.: It is important that society be educated to recognize normal and abnormal behavior. In general, it is easy to see that a man is psychotic, but it is difficult, for instance, to find the hidden traits behind the cool mask of the criminal. Psychiatrists have long been trying to get an insight into this problem, but much is left to be learned. All investigations, including such studies as Dr. Kaufman's, deserve attention. The ideal that all offenders be given a psychiatric examination is to be striven for. Under the present system this is impossible. However, there are two types of offenders, sex offenders and murderers, for whom a psychiatric examination before the court is of paramount importance. In Norway all such offenders are examined as a rule before they come to court.

Examination in court, might make possible, in addition more adequate individualization, proper placement of the offender. Since much crime is a result of immaturity, all criminals of immature type would, therefore, by proper classification be placed and educated in more suitable surroundings than the prisons. Even here it might be possible to provide education by psychiatrists and psychologists. For all these reasons, thorough examination of the offenders and greater collaboration with the court before trial would accomplish better results.

It may be that Dr. Roche is right in his assumption of the role of masochistic traits in criminal behavior, but it is difficult to understand how this can be in keeping with knowledge that masochistic and sadistic traits go hand in hand. True, in many cases the offender shows predominantly either sadistic or masochistic traits, but when sadistic and apparently less pronounced masochistic traits are present, or vice versa, one would in all probability find an interplay of the two components.

DR. JOSEPH C. YASKIN: Although I am not a student of criminology, some challenging statements made this evening were of interest to me as a neuro-psychiatrist. As I understand it, Dr. Roche believes that masochism plays an important role in the psychopathologic makeup of the criminal. Dr. Staub believes that the psychologic condition of the criminal does not differ materially from that of the psychotic, the psychoneurotic or the neurotic person. From my study of the psychoneuroses, I have felt that masochism is a mechanism one can frequently detect in psychopathologic conditions of many kinds. I, therefore, feel that masochism does not play any primary role in the psychopathology of the criminal.

I do not believe that sordid early environment is an important factor in the development of the criminal. I cannot escape the observation that many such persons have certain fundamental difficulties, perhaps inherited. It reminds me of a child whom I began to observe at the age of 10 or 11 years and who, at the age of about 14, committed some pretty serious crimes. This boy exhibited no anxiety regarding his misdoings. I cannot forget the statement that Judge Brown made, "I am going to give this fellow a break, but no matter what you or I, or any one else, does for this boy, he is headed for the penitentiary." In this connection, Dr. Gerald H. J. Pearson, who studied the aggressive child, came to the conclusion that such a child exhibits trends not ascribable to environmental factors and not correctable by any form of therapy.

One cannot escape the conclusion that in handling criminals society needs jails, just as it needs hospitals for the mentally ill. I do not mean to convey the idea that the jail offers the best mode of treating the criminal, any more than I believe that the hospital for the mentally ill is the best place for treating the insane.

DR. DANIEL J. MCCARTHY: With respect to the relation of the psychiatrist to the court, the rigid attitude of the court and the test of the sane and the insane grew out of the laxity of the English courts, where so many persons were being relieved of the responsibility of their crimes. In the McNaughton case, the test of right and wrong was brought out, and agreement on the matter of mental disorder was reached. I agree that the whole problem of crime is one of mental disorder; certainly, it is a matter for the psychiatrist. For eighteen or twenty years Judge Brown, of the Municipal Court of Philadelphia, has worked on the

assumption that it is better that the judge have a complete knowledge of the case before, and not after, the trial, and that the offender be stamped as a criminal before that time. On the bench one wonders about the family history, the physical health, the environment and the psychologic factors. If the history is before the judge, he can ask intelligent questions of the attorney and is equipped with better knowledge before the matter goes to the jury. It is not sufficient to have the psychiatrist's judgment after the case is tried, and before the man is sentenced; the study should be made before the case is tried.

To go back to Dr. Roche's belief that one might solve the crime situation by educational and psychiatric means, one has only to sit in the court day after day to learn that some criminals are real criminals and that criminality is inherent in their protoplasm. But no generalized rules may be laid down; every case is different, just as in every case the physician studies in his office.

DR. SAMUEL LEOPOLD: The need of psychiatric examination in cases in the criminal court needs no argument. I am glad progress is now being made in this respect. Dr. McCarthy has so well expressed the views of the members on the subject that it is not necessary to repeat them.

The stress that Dr. Roche places on the masochistic motives in criminal behavior seems exaggerated. The average criminal is a practical man, in contact with mundane things, so that his feeling of guilt and need for expiation are, to say the least, very limited. I can see that there might be an occasional compulsive state with which masochistic behavior might be tied, but it is rare.

JUDGE CHARLES L. BROWN: Dr. McCarthy has overemphasized what my associates and I have been doing for a number of years. We do become familiar with the mental, physical and environmental conditions of children and adults who come into the social branches of our court. I have received many ideas from eminent physicians. At the time of the establishment of the Medical Advisory Board, Dr. Charles Penrose, the chairman, said to me: "Judge, I think you are doing a fine piece of work, but what of the physical and mental condition of those charged with crime and other offenses against the law? You do not know the first thing about the criminal that comes before the court. It is not possible to make an investigation of the environmental, physical or mental status prior to the trial. I suggest that, if at all possible, sentence be postponed until you can make such an investigation and submit your report to the judge as a guide in the passing of judgment." This we have been doing since 1917. Of course, I do not think one should become too tender about the punishment of crime. Society ought to be protected, and one should not be too morbidly interested in a man who is judged antisocial. Particularly, society should be better protected against the feeble-minded delinquent.

JUDGE GERALD F. FLOOD: The court has used psychiatric assistance in a number of cases, I believe not more than 40 out of 100, and a great deal of good has come from the material. Quarter Sessions Court does not have such a service, but I believe that all agree that it should. At present, when my colleagues and I encounter a case of sex offense we are confused; we know little about the background and usually have to defer sentence until a psychiatric examination is completed. Usually the report is returned to us in a week, and in the meantime we have forgotten a great deal about the offense and the atmosphere of the courtroom while the trial was going on. The psychiatric examination is important, but I believe there is something much more important that has not been worked out in Philadelphia—the differentiation of institutions to which the offender is sent after judgment has been passed on him.

DR. PHILIP Q. ROCHE: At the outset, I should like to say that it is my intention to convey the idea that masochistic motives are more often the basis of criminal behavior than is commonly suspected. One is accustomed to think of crime in terms of criminal aggression against the public, and is less mindful of the criminal's aggression against himself. When one examines a criminal in terms of irrational aggression against himself, one comes closer not only to a more satisfactory explanation of the criminal act but to a more effective approach to

treatment. In my experience, I have rarely obtained an adequate explanation for his act from the criminal or from the court, which has imposed punishment on him.

In this presentation I also emphasized that physical symptoms and misbehavior are but variants of the same psychic conflict, and I pointed out that their development at the threshold of parole, and often during parole, is not accidental, but is a meaningful indication that punishment alone has not secured the criminal against himself.

I surmise from comments of the discussants that my thesis proposes a soft indulgence of the criminal. I propose the abolition of punishment as a measured revenge of the community, but I do not propose that one do away with segregation. I propose that the criminal be segregated in the same way that the psychotic patient is removed from free circulation in the community, and that his restoration to the community be dependent not on a predetermined sentence but on nonjudicial agencies trained in the task of human appraisal and in the technic assisting the criminal (or the psychotic patient) in modifying his impulses to those within community tolerance. In this proposal I visualize the principle of the indeterminate sentence of the criminal as it is now, in effect, applied to the insane. In either case, one is dealing with a socially disabled person.

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, Oct. 15, 1942

Function of the Frontal Lobe in Man: The Dynamic Visual Field. DR. WARD C. HALSTEAD (by invitation).

The dynamic visual field is that portion of the peripheral retinal field that can be made to yield a threshold visual impression at the same instant that a form discrimination is being made in the region of the fovea. It has been mapped in normal persons and in carefully selected patients with unilateral neurosurgical lesions who had no ocular disturbance. For exposures as brief as twenty to fifty milliseconds, the dynamic visual field was found to correspond with the campimetric field in normal subjects and in patients with a large lesion of the occipital or the parietal lobe with associated hemianopia. Patients with a lesion of the frontal lobe had normally full campimetric visual fields. Their dynamic visual fields were greatly constricted, however, even when exposures as long as eighty to one hundred milliseconds were employed. For certain types of visual situations it may thus be demonstrated that the patient with a unilateral lesion of the frontal lobe has available quantitatively less visual field than the patient with homonymous hemianopia associated with a large cerebral lesion posterior to the frontal lobe. The relation of this observation to results which other investigators and I have previously reported is discussed.

This paper will be published in full.

Encephalitis Associated with Herpes Zoster: Report of a Case. DR. SIGMUND KRUMHOLZ and DR. JOSEPH A. LUHAN.

A housewife, aged 58, who had previously been in fairly good health, on March 7, 1942 had severe pain in a cutaneous area, which two days later became the seat of a herpetic rash, limited to the lower part of the face, the neck and the upper part of the shoulder and chest on the left side. A dermatologist confirmed the diagnosis of herpes zoster. On April 5 the patient became mentally disturbed. Examination the next day by one of us (S. K.) revealed she was moaning and restless and out of contact with the environment. The rectal tem-

perature was 104.6 F. The lungs were clear. Although the patient was unco-operative, there was no detectable paralysis of the cranial nerves or the extremities, and the reflexes were normal. The spinal fluid contained 40 cells per cubic millimeter, 80 per cent of which were lymphocytes. The patient continued to be noisy and restless; and her illness ran a febrile course, and she died on April 15, ten days after onset of the cerebral symptoms and thirty-nine days after appearance of the zoster.

Necropsy revealed fibrinous pericardosis, advanced parenchymatous degeneration of the myocardium and terminal bronchopneumonia. The spinal cord was not obtained. Histologic examination of sections from many blocks taken from all lobes of the brain, the subcortical white matter, the basal ganglia and the hypothalamus revealed only edema and hyperemia of the leptomeninges, "acute ganglion cell disease" in the cortex and a hydropic state of the white matter underlying the ependymal surfaces. The medulla, on the other hand, was the seat of a meningoencephalitis, characterized by (1) mild perivascular infiltrations of lymphocytes; (2) tissue foci, principally in the olives and the cuneate nuclei, containing numerous microglial polyblasts and showing cellular destruction, neuronophagia and capillary hyperplasia, and (3) small patches of demyelination, especially near one of the olives. The pons and midbrain appeared to be uninvolved.

The noninfiltrative changes in the cerebral cortex were like those seen in some cases of toxic encephalopathy. The question arises whether both these lesions and the anatomically demonstrable nonsuppurative meningoencephalitis inferior were produced by one etiologic agent, the virus of herpes zoster. It is reasonable to ascribe the medullary process to upward dissemination of this neurotropic virus, which entered the cord through the cervical roots.

DISCUSSION

DR. MAURICE OPPENHEIM: When I saw the patient on April 5, in consultation with Dr. C. R. Windmueller, she was in bed, screaming, extremely restless and in poor general condition in consequence of lack of food. There was no doubt of the diagnosis of herpes zoster, which had been made by Dr. Windmueller. On the left side, the lower part of the face, the neck, the pectoral area and the scapular region were involved. Red spots of various sizes, with scars in the center, were noted. Six weeks after onset the herpetic blisters were entirely gone, and the subsequent nervous condition developed. Dr. Krumholz agreed with me in suspecting encephalitis.

Three forms of herpes are encountered in dermatologic practice, of which two are often confused, herpes zoster and herpes simplex zosteriformis; herpes simplex is easily diagnosed. It would not be surprising to see encephalitis follow herpes simplex, for experimental studies on rabbits have shown that the infection can spread to the cord and involve the brain. Herpes zoster is clinically different; many crops of blisters follow in succession. The infection cannot be transmitted to the cornea of the rabbit. Herpes zoster also shows complement fixation with the serum from blisters of herpes zoster, whereas herpes simplex does not. Patients with herpes zoster usually recover, without relapse; with herpes simplex they frequently succumb.

Many authorities believe that herpes zoster and chickenpox are caused by the same virus, and it is known that chickenpox is sometimes followed by encephalitis. Bokai was the first to advocate this hypothesis. Osler reported cases in which encephalitis followed the final stage of chickenpox.

In the present case the herpes zoster had entirely disappeared six weeks after the onset. My first impression was that the nervous complication was meningitis, which sometimes follows herpes zoster. This case could be used as proof of Bokai's theory that chickenpox and herpes zoster are caused by the same virus—the herpetic virus, a neurotropic and dermatotropic virus. It may be, therefore, that herpes zoster in some cases is followed by encephalitis. In postvaccinal encephalitis, which may occur nine to thirteen days after vaccination, the virus

belongs to the same group. This case was a typical instance of herpes zoster, and not of herpes simplex zosteriformis.

DR. GEORGE B. HASSIN: I do not understand how one can associate herpes zoster with cerebral manifestations that occurred weeks after its onset. In Thalheimer's case the interval was six weeks, and for this reason some authorities do not consider it one of herpetic encephalitis. In the case I observed the cerebral symptoms were coexistent with a herpetic eruption along the distribution of the fifth nerve, and it has been shown experimentally that encephalitis can be produced in rabbits by inoculation of the cornea with herpes virus. Kuttner, among others, emphasized that herpetic encephalitis differs from the epidemic type and that it is a specific morbid entity.

The changes in the brain in this case have been well demonstrated by the authors, who stressed the edema and perivascular infiltrations in the medulla. The edema was much more pronounced than the infiltrations and generally, in my opinion, is of greater importance than changes in the vessels or the ganglion cells. The condition of the subependymal areas and the ventricles themselves should be of great interest.

Eonism: Report of a Case with Additional Outstanding Psychopathic Features. DR. D. M. OLKON and DR. IRENE CASE SHERMAN.

An outstanding type of sexual abnormality is eonism, or transvestitism. Many investigators have reported cases from history, from police records and from their own experience, under a variety of designations referring to the same type of personality anlage. Hirschfeld's *Transvestite* was classified by Krafft-Ebing under fetichistic personality; Havelock Ellis called it eonism, or sexesthetic inversion; by still others it has been included under the caption of homosexuality. All designations, however, are for the purpose of establishing the psychopathic trends in the personality.

A case history was given; the patient's autobiography was read, and photographs were presented. Physically, the patient was normal. His hair was long, well groomed and carefully waved. He had worn women's clothes constantly for the past seven years. By psychologic tests his intelligence rating was average. The results of the Rorschach test were indicative of a compulsive neurotic personality. He asked to be certified as a female and to have his genitalia amputated and a vagina constructed.

Terminology in this case was inadequate, as the patient presented many more abnormalities of personality than his dressing in female attire. The novelty was the multiplicity of tendencies, which could hardly be understood from orthodox designation. He showed evidences of narcissism, exhibitionism, fetishism, masochism and sadism and was homosexual. In addition, he was lacking in emotional response and social sensitiveness, showed no evidence of shame or regard for the opinions of others and rejected all responsibility to society. This dichotomy of trends makes the case unique.

DISCUSSION

DR. IRENE CASE SHERMAN: The patient was referred to the Illinois Neuropsychiatric Institute from the draft board, after having appeared there in female attire. Physically he was normal in every respect. The physical proportions were of masculine type; the chest was broad, and the hips were narrow. The distribution of hair, also, was masculine. The skin was rather fine, but the hair was of average coarseness. He was proud of his hair and had it waved at a beauty salon regularly. The only occasions on which he had been arrested were when he was in male attire, because the long hair attracted attention. When he went about dressed as a woman, he was not apprehended.

His intelligence quotient was 95. In the Rorschach test he gave an unusually large number of responses, with a great deal of detail. This was interpreted as indicative of a compulsive-obsessive type of neurotic personality. There is little

information on the dynamics of his behavior. Assays of the hormonal content of the urine were not made, because he refused to cooperate. He is much opposed to any glandular treatment because he wishes to be a woman.

DR. RALPH HAMILL: I do not know about diving into this whirlpool of the question of boy and girl. I have worked about twenty years with children, and I have concluded that every boy wants to be a girl and every girl a boy. As I interpret it, the boy takes with a great deal of chagrin the fact that the girl can have a baby and he cannot. Every boy up to the age of 12 whom I have been able to get close to has told me he wanted to be a girl; that is so surprising that I have tried to think of some reason. As far as I can explain it, every boy gets used to his own body and wants to know about another kind of body, and the only way to know it is to be it. Consequently, the matter gets out of the realm of sex and into that of knowledge.

It seems to me that this fact is an important element in mental disease. After puberty, when function has determined what structure has only suggested up to that time, the idea is ridiculous. But the ridiculous is the crazy, an important element in schizophrenia. It is a remnant of childhood that gets into the sexual field, and one can ridicule it; nevertheless, it is important.

Book Reviews

Lectures on Conditioned Reflexes: Volume II. Conditioned Reflexes and Psychiatry. By Ivan Petrovitch Pavlov. Translated and edited by W. Horsley Gantt, M.D., B.Sc. Price \$4. Pp. 199. New York: International Publishers, 1941.

This volume contains all of Pavlov's lectures on conditioned reflexes from 1928 to his death in 1936. With volume I (1903 to 1928) the English reader has a complete collection of Pavlov's lectures on this subject. Gantt has done the difficult task of translation with credit. Moreover, he has written a twenty-eight page introduction, in which he discusses the history of Pavlov's research and gives a critical evaluation of his work. Best of all is the appreciation of the man himself, in the section entitled "Closing Years." Here one senses what a really great figure Pavlov was—his energy, his enthusiasm and his ability to plan. In 1935 he told the International Congress in Moscow: "I am an experimenter from head to foot. My whole life has consisted of experiments." And in 1936, in a letter to young scientists, he insisted on the importance of systematic planning: "From the very beginning of your work, train yourselves to be strictly systematic in amassing knowledge."

The main body of the book is composed of fifteen lectures on conditioned reflexes or the application of the principles of conditioning to psychiatry and psychology. The best of the lectures are those dealing with his own physiologic work, summaries that bring out his discoveries and principles, such as chapter XLIII, "A Brief Outline of the Higher Nervous Activity," and chapter XLIV, "Contributions to the Physiology and Pathology of the Higher Nervous Activity," and his own story of the investigations and concepts in chapter LVII, "The Conditioned Reflex," written in 1935. These are important contributions from a great man that should be in every library of neuropsychiatry.

Pavlov is at his worst when he speaks of the clinical field. As Gantt says in the translator's preface, "It is not the fortune of many to explore a fresh field of inquiry after the age of seventy-five." In this he tells of his explorations into the domain of psychiatry—perhaps it was a misfortune. Although he is tentative in his writing, as in chapter XLII, "Trial Excursion of a Physiologist in the Field of Psychiatry," he sometimes makes bold statements on what to a clinician would seem like inadequate evidence. For instance, "studying the aforementioned schizophrenic symptoms, I came to the conclusion that they are the expression of a chronic hypnotic state." With somewhat more reason he connects hysteria with hypnosis (chapter LII). In chapter LV, "An Attempt at a Physiological Interpretation of Obsessions and of Paranoia," he shows that he has read extensively on paranoia and describes some cases, admitting frankly that he is no clinician. He wishes merely to bring out that "psychiatrists in their respective domains, will inevitably have to reckon with the following fundamental pathophysiological fact: the complete isolation of functionally pathological (at the aetiological moment) points of the cortex, the pathological inertness of the excitatory process, and the ultra-paradoxical phase." To accept this point of view at all one must believe that brains may be "strong" or "weak" (neither of these terms is sufficiently defined) and that the cortex is made up of a mosaic of interrelated excitatory and inhibitory points.

Mental Health in College. By Clements C. Fry, M.D., with the collaboration of Edna G. Rostow. Price, \$2. Pp. 365. New York: Commonwealth Fund, Division of Publications, 1942.

This book is a useful effort directed toward altering of the policy of the more backward institutions of higher education the student health services of which do not yet include those of a psychiatrist. It should prove helpful to the college dean, the bewildered parents of an errant college youth, the teacher who wonders why some students may fall far short of the promise given, the psychiatrist interested in adolescents or the campus physician who finds no clue to troublesome symptoms.

Dr. Fry has been associated with Yale University in the capacity of psychiatrist since 1926. The material of the book draws on the case histories of 1,257 students seen by the student health service during the ten years prior to 1942.

Approximately half the volume is concerned with problems of personality growth, divided into two chapters, the first dealing with problems of family relationships and the second with sexual growth, behavior and attitudes. College students, however, are a special group of adolescents, subjected to the peculiar strains of the university, with its characteristic organization, traditions and mores. In his dealing with problems of this order, the object of the psychiatrist is in a general sense an educational one, for he is interested in furthering the growth of the student's character.

Another portion of the book concerns itself briefly with reactions to the undergraduate environment. It deals with a description of the complexities of organization of Yale's various schools, the college plan and the social significance of fraternities, senior societies and honor societies. Scholastic adjustment and social adjustment are dealt with at greater length, and, as always, principles are illustrated admirably with case histories. To know that many maladjustments are inevitable when any group of persons tries to adjust to a new environment should serve as incitement to discovery of personality difficulties among students as early as possible in order that the psychiatrist may assist individual students to achieve a satisfactory adjustment and thereby increase their efficiency and the productivity of their college experience.

The last section of this volume deals with the problems found in the graduate and professional schools. Dr. Fry speaks deprecatingly, in small print, of the therapeutic effects of psychoanalysis seen in a small group of students, and wistfully, in larger print, of the peculiar resistance of medical students to psychiatry. The author is deeply appreciative of Dr. Adolf Meyer's influence in the development of his psychobiologic approach to these problems of mental hygiene.

The book is recommended for college physicians.

Love Against Hate. By Karl Menninger, M.D., with the collaboration of Jeanetta Lyle Menninger. Price \$3.50. Pp. 311. New York: Harcourt, Brace and Co., Inc., 1942.

In the introduction Menninger states that he deliberately chose to write this book for any intelligent person, professional or nonprofessional, rather than for the specialist. He states, however, that the substance of his book is what he teaches his students and discusses with his colleagues. In my opinion, the book is readable, the style is polished and the content is of value not only to the lay public but to professional persons, including other psychiatrists. The purpose of the book is to show the resources which one has at one's command to favor the life (love) instinct and to oppose the death (hate) instinct. In the first four chapters the author describes the frustrations of the child, the frustrations of women and the deprecation of femininity. The chapter dealing with frustrations of the child is well presented and contains material widely accepted by the psychiatric profession. In the chapter on frustrations of women, Menninger points out that women frustrate their children because they themselves have been

frustrated by civilization in general, and by men in particular, by means of political, economic and legal codes which keep them in abeyance. They are frustrated frequently in their sexual life and are often deprived of the experience of pregnancy and childbirth. In a subsequent chapter, the author points out ways in which a woman identifies herself with the male aggressor and then depreciates her own femininity.

In the second half of the book the author suggests five solutions for these problems, namely: work, play, faith, hope and love. Each of these five topics is described at some length in the individual chapters. Work is described as being of the greatest importance as a method of absorbing the aggressive energies of mankind in a useful direction, and the author points out ways in which work can be pleasurable. He emphasizes the need of vocational education and the failure of most psychiatrists and analysts to support these aims. In the chapter devoted to play, he describes various play technics used with children and adults with mental disorders and illustrates recreational outlets for normal persons in card playing, dancing, art, music, etc.

The book contains many short but valuable case histories and has an adequate bibliography. In my opinion, the book is to be highly recommended.

Our Age of Unreason. By Franz Alexander, M.D. Price \$3. Pp. 341. New York: J. B. Lippincott Company, 1942.

This book is an attempt by a psychoanalyst to understand and explain the chaos of the present day world.

The volume is divided into three sections, entitled "Reason to Unreason," "The Fundamentals of Human Behavior" and "From Unreason to Reason." There is a 130 page survey of the world's history, particularly that of Germany, as well as a brief survey of the philosophies and psychologies of the various countries at war. These summaries are superficial. At one point the author emphasizes the need for psychoanalysts who are physiologists, historians, anthropologists and sociologists and who will apply psychoanalysis to the study of biologic and social processes. Any one entitled to consider himself a specialist in such a wide field of interest would be a rare person. The need for such persons is real.

It must, however, be noted that the book is a sincere attempt to approach the problem of world chaos from a new viewpoint in order to explain the irrational behavior of the world. The author relates the nationalistic irrational behavior of some countries to the unconscious aggressions which are never expressed in a totalitarian state. He indicates that in the development of Germany there was a rapid change from a feudal to a modern industrialized national state, all in a historically brief period. This led to a paternalistic attitude, which suppressed all hostile impulses in the individual. These impulses, in turn, were directed outwardly against other countries. In a democracy, with its slower development and freer play of emotions, there is less inner tension in the individual, and therefore less need for destruction of a neighboring country. For the layman, the book offers a different interpretation of the present day world situation. For the student of neurology and psychiatry, it is a superficial study.

Introduction to the Psychoanalytic Theory of the Libido. By Richard Sterba. Nervous and Mental Disease Monograph Series, No. 68. Price \$2. Pp. 81. New York: Nervous and Mental Disease Publishing Company, 1942.

The author feels that psychoanalysis faces a real danger, for he sees in the "culturalist school" a disregard of the libido theory, which he considers one of the basic concepts in freudian psychoanalysis. It is with this thought in mind that the book is written as a "timely recapitulation" of Freud's observations concerning the instincts. It appears to us that this book has a *raison d'être* more plausible than as a defense against attacks on the libido theory. For one who has

read the basic material on instinct and libido, there is nothing new in this book. However, for the beginner who would like some more continuous presentation of the libido theory than he would get if he went to the sources, this book serves a useful purpose. One would get the impression from the preface that the author planned to take up the cudgels in defense of the libido theory, but one finds no pro and con presentations in this book, and other theories and viewpoints are not discussed.

The author presents in a simple and clear style the freudian concepts of instincts, with special attention to the sexual instinct. He discusses the various well known phases of development of the libido, utilizing Abraham's modifications. In addition, there are chapters on narcissism, the vicissitudes of the instincts and, finally, the repetition compulsion and the death instinct. All of this is presented in a readable and simple fashion. The book would have benefited considerably by having a good bibliography. ♦

STUDIES IN DISEASES OF MUSCLE

XII. HEREDITY OF PROGRESSIVE MUSCULAR DYSTROPHY; RELATIONSHIP BETWEEN AGE AT ONSET OF SYMPTOMS AND CLINICAL COURSE

A. T. MILHORAT, M.D.

AND

H. G. WOLFF, M.D.

NEW YORK

Progressive muscular dystrophy is generally regarded as a "hereditary disease" because patients with this condition frequently give a history of other members of the family who have been similarly affected. Numerous families have been reported in which the disease has appeared in different generations, but the genealogic studies thus far have been too few and incomplete. In consequence, the mechanism of the hereditary transmission of progressive muscular dystrophy is still imperfectly understood. The difficulties usually encountered in obtaining data on heredity in human beings are considerably increased in the case of progressive muscular dystrophy. Unlike conditions, such as hemophilia and color blindness, which can always be demonstrated early in life in affected persons and of which the mode of hereditary transmission is well understood, progressive muscular dystrophy need not manifest itself until later in life. Therefore, members of the family who are without symptoms cannot be considered free from the disease until they have passed an age at which the development of the disease would appear improbable. Moreover, patients in whom symptoms of progressive muscular dystrophy develop before the third decade usually have no descendants.

In the present state of knowledge, the publication of factual information is important. The elucidation of the problem will be possible only when a sufficient number of "dystrophy families" have been followed through several generations, or when large numbers of less complete family trees have been studied. It is for this reason that the present data are reported.

MATERIAL AND METHODS

During the past twelve years a large number of patients with progressive muscular dystrophy were examined. For 86 of these all available information regarding the hereditary transmission of the disease was obtained. These patients were members of 75 different families, in which 39 additional members were affected with the disease—a total of 125 persons on whom data regarding the heredity of muscular dystrophy were ascertained. In all instances in which it was possible other members of these families were examined for evidence of the disease. The importance of examining other members of affected families was emphasized on a few occasions when relatives alleged to have progressive muscular dystrophy were found instead to have some unrelated condition. Practically all of the 86 patients who were examined were followed at regular intervals over long periods. In addition, metabolic studies were made on many of these patients at frequent intervals over periods of several years. All the information available on the remaining 39 patients, who were not examined by us, was obtained. Many of these patients had been examined in other hospitals or had been seen by other physicians, and in these instances full reports were requested.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc. From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

OBSERVATIONS AND COMMENT

Incidence of Positive Familial History.—The data are shown in the table. Of the 86 patients who were examined, 35 per cent gave a history of at least 1 other member of the family with the disease, and 54 per cent of the total series of 125 patients, which included all the affected members of the families investigated, gave a positive familial history of the disease. In 27 per cent of the 75 families investigated 2 or more members had muscular dystrophy; in each of the remaining 73 per cent of the families only 1 member was known to have had the disease.

These observations agree, on the whole, with those of other investigators. In only 14 of the 44 cases of pseudohypertrophic muscular dystrophy described by Gowers¹ did the patients come of families without muscular disease; the remaining 30 cases (68 per cent) were distributed among 10 families. Gowers found data on 176 additional cases in the literature, and of the total of 220 cases, 102 were without familial occurrence and 118 (53.6 per cent) were distributed among 39 families. Poore² reported 1 case and analyzed 85 cases in the literature. In 43 (50 per cent) of the total of 86 cases a positive familial history was obtained.

Data on Inheritance of Progressive Muscular Dystrophy in One Hundred and Twenty-Five Persons

Patients *	Number	Familial History		Sex Incidence		
		Posi- tive, %	Nega- tive, %	Males	Females	Ratio Males:Females
Examination.....	85	35	65	67	19	3.5:1
Data from examination and history.....	125	34	46	94	31	3:1
Heredity by simple sex-linked recessive factor †...	26	26	0	
Heredity by dominant factor.....	14	7	7	1:1
Heredity of undetermined type, including "spo- radic" occurrence and lineal inheritance.....	65	61	24	2.5:1
Lineal inheritance.....	27	14	13	1:1

* The patients were members of 75 different families; in 73 per cent of these families there was only 1 person with the disease, and in the remaining 27 per cent at least 2 persons were affected

† The muscular dystrophy appeared in the males but was transmitted by apparently healthy females.

Familial incidence was found in 42 per cent of the 36 cases described by Hurwitz.³ Sjövall⁴ stated that of 157 cases, 63 were isolated, giving a familial incidence of 60 per cent.

Sex Incidence.—There were 67 males and 19 females in the group of 86 patients who were examined. The ratio of males to females in this group was 3.5:1. Of the total series of 125 patients, 94 were males and 31 were females, a ratio of 3:1.

The sex ratio observed in this series was similar to that in most series previously reported. Weitz,⁵ in a compilation of 639 cases from the literature, found that males were affected two and nine-tenths times as often as females. These

1. Gowers, W. R.: *Pseudo-Hypertrophic Muscular Paralysis: A Clinical Lecture*, London, J. & A. Churchill, 1879.

2. Poore, C. T.: *Pseudo-Hypertrophic Muscular Paralysis, with an Analysis of Cases*, New York M. J. 21:569, 1875.

3. Hurwitz, S.: *Primary Myopathies: Report of Thirty-Six Cases and Review of the Literature*, Arch. Neurol. & Psychiat. 36:1294 (Dec.) 1936.

4. Sjövall, B.: *Dystrophia musculorum progressiva: Eine Erblchkeitsmedizinische und klinische Studie*, Acta psychiat. et neurol. (supp.) 10:1, 1936.

5. Weitz, W.: *Ueber die Vererbung bei der Muskeldystrophie*, Deutsche Ztschr. f. Nervenl. 72:143, 1921.

cases represented various clinical types of muscular dystrophy. In the series reported by Funsten⁶ there were 25 males and 5 females. Grothaus⁷ studied 30 patients with progressive muscular dystrophy in the surgical clinic at Freiburg, Germany, and, by means of church records, investigated the family trees of the patients back to 1800. The records went back 9 generations, but only those of 5 generations were used. In the series of patients examined by Grothaus the ratio of males to females was 3:1, but for the 257 persons for whom data were obtained from the family records the ratio was 1.4:1. Sjövall⁴ found a ratio of males to females of 2:1 in the records of 157 patients who had been seen in several

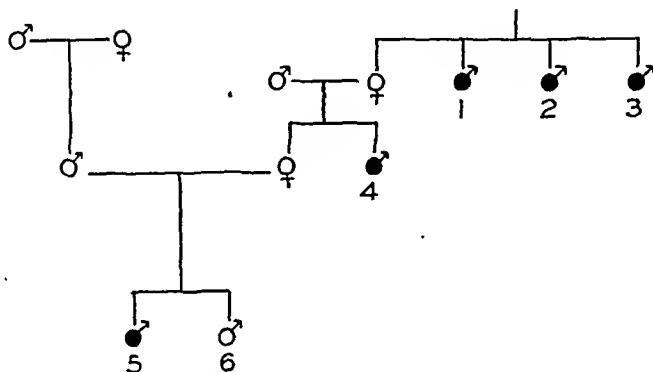


Fig. 1.—Patient 5, aged 8 years, had a moderately advanced condition, with onset at the age of 2 years. Sibling 6, aged 7 months, was without muscular involvement. Subjects 1, 2, 3 and 4 had onset of muscular symptoms in childhood and became totally incapacitated at about puberty.

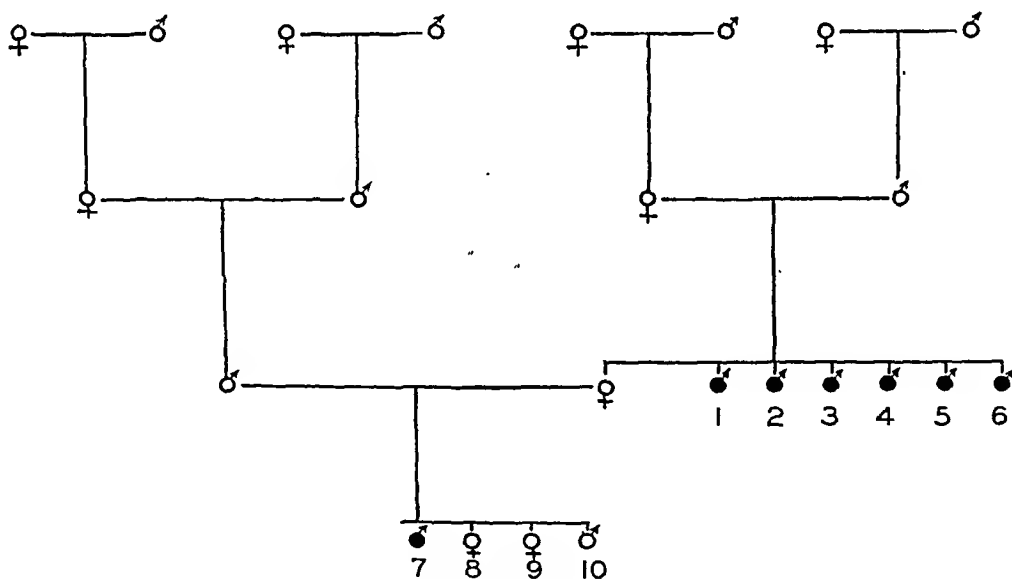


Fig. 2.—In patients 1 to 6 dystrophy developed at the age of 7 years. Patient 1 died at the age of 20, of pulmonary infection, when muscular disability was far advanced. Patients 2, 3, 4 and 5, aged 23, 18, 16 and 13 years respectively, are unable to walk or stand. Patient 6, aged 11 years, can still walk, although with difficulty. Patient 7, aged 5½ years, first showed symptoms at the age of 2 years. His siblings, 8, 9 and 10, are 4½, 2½ and 1½ years old respectively.

clinics in Lund, Stockholm and Uppsala, Sweden, during the years from 1910 to 1930. The patients were members of 105 families. A considerably higher

6. Funsten; R. V.: Muscular Dystrophy, *J. Bone & Joint Surg.* 5:190, 1923.

7. Grothaus, E.: Untersuchungen über den Erbgang der Dystrophia musculorum progressiva (Erb), *Arch. f. klin. Chir.* 181:344, 1934.

sex ratio was reported by Hough,⁸ Mettel and Slocum⁹ and Voshell.¹⁰ In each of the series of 43 and 48 patients observed by Hough and by Mettel and Slocum, respectively, there was only 1 female. Voshell reported that in his experience of about 25 cases only 2 females were seen.

However, in instances in which inheritance is by a dominant factor both sexes usually are affected with equal frequency. Thus, in this series, for the 14 patients in whom inheritance of the disease was dominant the sex ratio was 1:1. A similar sex ratio was seen in the family reported by Pearson.¹¹ Eight members in 4 generations were affected; of these, 4 were males and 4 females.

Types of Hereditary Transmission.—In 26 males in the total of 125 patients the inheritance of progressive muscular dystrophy was by a simple sex-linked recessive factor. Two of the family trees are shown in figures 1 and 2. These 26 patients were members of 5 of the total of 75 families in this series. In these 5 families males alone were affected, the gene containing the factor for muscular dystrophy

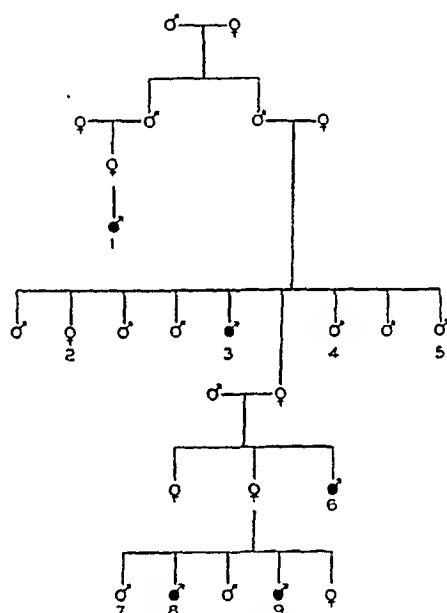


Fig. 3.—Patients 3, 6 and 9 had muscular dystrophy, with onset at the ages of 7 to 10 years; patients 3 and 6 died at 15 years of age, of pulmonary infection; patient 9 died at the age of 14 years, after an operation for acute appendicitis. Patient 8, aged 9 years, with moderately advanced dystrophy, first had symptoms at the age of 7 years. Subject 1 is said to have had dystrophy, but the diagnosis is not certain.

having been transmitted by apparently healthy females to their affected sons. All the mothers of these patients had male siblings with the disease. In 3 of the families every male descendant on whom data were available had muscular dystrophy. However, in 1 family (fig. 3) the disease developed in only 4 out of a total of 12 males in 3 generations. In addition to these affected members, 1 male descendant on the maternal great-grandfather's side of the family is said to have had muscular disability similar to that of our patient (8, fig. 3). In another family

8. Hough, G. De N.: Two Cases of Atypical Familial Dystrophy, *New England J. Med.* **206**:396, 1932.

9. Mettel, H. B., and Slocum, Y. K.: Pseudohypertrophic Muscular Dystrophy: Preliminary Report on the Treatment of Three Cases with Glycine, *J. Pediat.* **3**:352, 1933.

10. Voshell, A. F.: Progressive Pseudohypertrophic Muscular Dystrophy, *South. M. J.* **26**:156, 1933.

11. Pearson, K.: Two New Pedigrees of Muscular Dystrophy, *Ann. Eugenics* **5**:179, 1933.

4 out of a total of 9 males had muscular dystrophy (fig. 4). The latter family is of considerable interest in that the mother of our patients was twice married and had a son with dystrophy by each of the husbands. The issue of the second marriage was twins; the girl has shown no muscular symptoms, whereas dystrophy developed in the boy. The mother showed no evidence of the disease, but her brother had muscular dystrophy. An apparently healthy sister of the mother had a son who became affected with the disease. In another family 2 females of a sibling group of 4 females and 3 males had dystrophy; 1 of the apparently healthy females

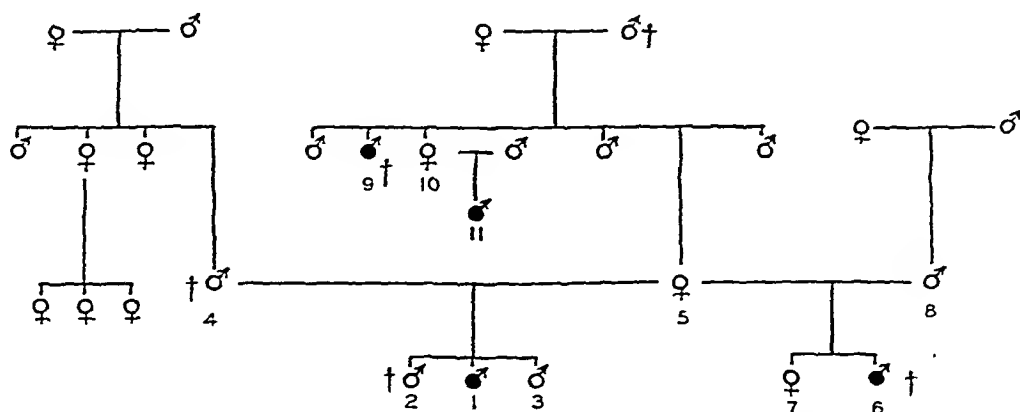


Fig. 4.—Patient 1, aged 10 years, with pseudohypertrophic muscular dystrophy, had onset of symptoms at the age of about 5 years. A brother (2) died at 3 months of age, of diarrhea. Another brother (3), aged 8 years, is normal. The father (4) was well until his death, at the age of 33, of appendicitis. The mother (5), aged 30, has no muscular symptoms. A step-brother of the patient (6) had dystrophy and died at the age of 2 years, of pertussis; a twin sister of this child (7), now aged 3 years, is normal. The father of these twins (8) is well, at the age of 28. Subject 9 had dystrophy and died at the age of 19. Subject 10, aged 39, is normal but has a son (11) with muscular dystrophy. (1 was a patient in the children's clinic, the New York Hospital. Dr. Samuel Z. Levine gave us permission to publish these data.)

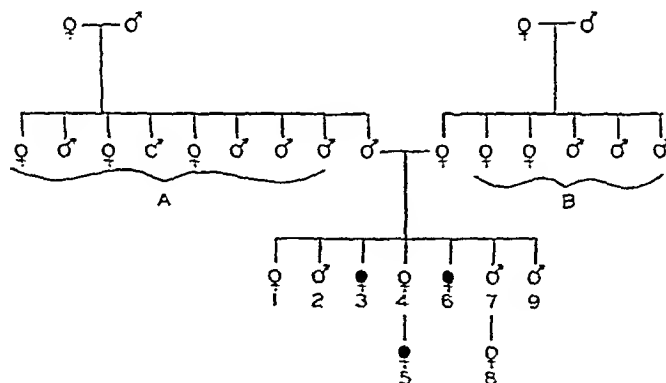


Fig. 5.—Members of groups A and B showed no evidence of muscular disease. All had several children, all of whom were normal. Subject 1 died at the age of 5 years, without muscular symptoms. Subjects 2, 4, 7, 8 and 9 are well at the ages of 32, 27, 34, 1 and 30 years, respectively. Patient 3 is 18 years old and has moderately advanced muscular dystrophy. Patient 5, aged 5 years, has had progressive muscular weakness since the age of 1 year, and has difficulty in walking. Subject 6, aged 29, showed generalized weakness at the age of 2 years. Her muscular dystrophy is now advanced.

of this group had a daughter in whom the disease developed. In this instance heredity was by a recessive factor which was not sex linked (fig. 5).

In 14 patients inheritance of the disease can be interpreted as having been by a dominant factor. Each patient had a parent who was affected by the disease, and all descendants of healthy parents were free from all evidence of muscular dystrophy. The 14 patients were members of 2 families. In 1 family a father and

his son were affected (fig. 6); in the other family there were 6 males and 6 females with muscular disease (fig. 7). In all of these patients the disease had its onset relatively late in life. Thus, in the family illustrated in figure 6, symptoms first were noted by the father at the age of 52 and by the son at the age of 15 years. In the second family in which the muscular disease was inherited by a dominant factor the average age of the patients when symptoms first were noted was about 33 years. The muscular involvement in the affected members of this family was unusual for dystrophy in that the muscles earliest and most severely involved were those of the calves and feet. The complete data, which are presented in the next

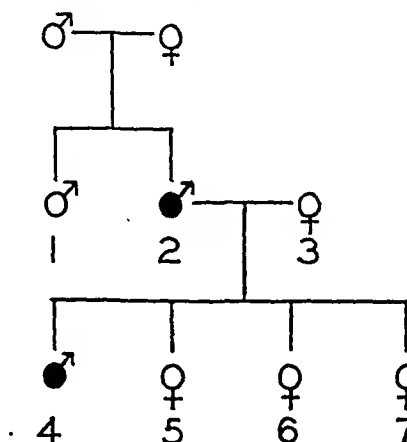


Fig. 6.—Subject 1, aged 59 years, is strong and healthy. Patient 2, aged 56, has wasting of the triceps muscles and the muscles of the calves and thighs; the calves are moderately enlarged; he "climbs up on himself" when straightening his body; his weakness started insidiously at the age of 52 to 53 years. In patient 4, aged 25 years, the condition started at the age of 15 years with wasting of the thigh muscles; later the muscles of the arms and hands became wasted.

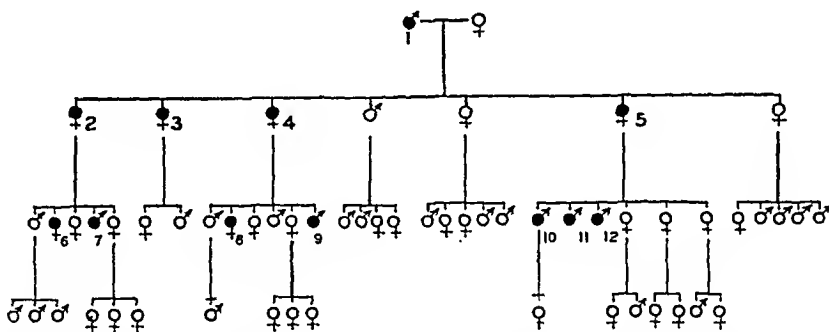


Fig. 7.—Family tree showing distal type of progressive muscular dystrophy with dominant type of heredity. Data on members of the family will be given in the next report on this series.¹²

report of this series,¹² indicate that the condition was an atrophic distal type of progressive muscular dystrophy.

Twenty-seven patients, including 14 males and 13 females, had at least 1 other sibling with dystrophy, but a history of the disease in preceding generations could not be obtained (figs. 8, 9, 10 and 11). Fifty-eight patients, of whom 47 were males and 11 females, gave a negative history for any other instance of the disease in their families.

12. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: XIII. Progressive Muscular Dystrophy of Atrophic Distal Type; Report on a Family; Report of Autopsy, *Arch. Neurol. & Psychiat.*, this issue, p. 655.

A summary of the observations on the types of inheritance is shown in the table. For 26 patients the evidence seems conclusive that inheritance was by a simple sex-linked recessive factor, similar to that for color blindness and hemophilia. All of these patients had dystrophy of the pseudohypertrophic type, and in all, the onset of the disease was in the first decade of life. In 14 other patients inheritance was by a dominant factor (figs. 6 and 7). Leiter¹³ reported on a family in which inheritance was dominant in the last 2 generations, whereas it appeared to be recessive in the preceding generation. Grothaus⁷ expressed the opinion that a recessive factor can in its transmission change to a dominant one. However, the mode of inheritance in the family whose tree is shown in figure 7 was uniformly dominant in the 3 generations on which data were available. Similarly, in the family reported on by Pearson¹¹ inheritance was dominant in 4 generations. Hansen and von Ubisch¹⁴ maintained that within the same family the type of hereditary transmission is uniform. Grothaus pointed out that the abortive forms of dystrophy often are dominant, and in the family reported on by Manson¹⁵ progression was slow. In the 14 patients reported on here, the onset of the disease was relatively late in life (ages from 28 to 43 years), and the

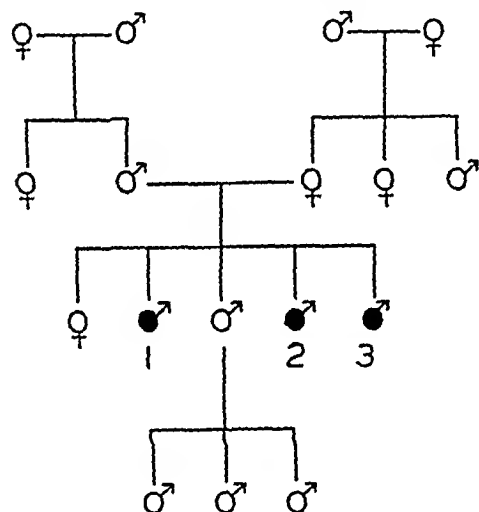


Figure 8

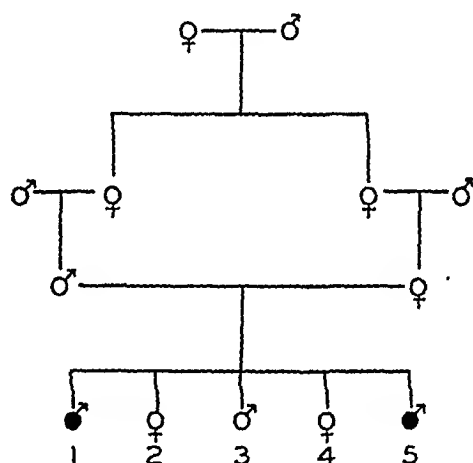


Figure 9

Fig. 8.—In patient 1, aged 22 years, the condition began at the age of 13 years; he is bedridden. Patient 2, aged 18 years, walks with difficulty; weakness was first noted at the age of 7 years. In patient 3 the condition started at the age of 14 years; the patient died at 28 years of age, of pneumonia, after being bedridden for four years. The normal male sibling is 30 years old and has 3 sons, the oldest of whom is 5 years of age.

Fig. 9.—The parents are first cousins. There is no known case of muscular dystrophy in the family except those of children 1 and 5. Patient 1, aged 21 years, is able to walk only with assistance; symptoms were first noted at the age of 5 years. Patient 5, aged 17 years, had onset of disability at the age of 5 years; his condition is far advanced. Siblings 2, 3 and 4 are normal.

symptoms progressed slowly. In a few instances the disease appeared to be abortive. In any event, it is obvious that muscular dystrophy when inheritance is dominant will not be transmitted and therefore will disappear from a family

13. Leiter, A.: Die Adrenalinbehandlung bei progressiver Muskeldystrophie, *Monatschr. f. Psychiat. u. Neurol.* **81**:289, 1932.

14. Hansen, K., and von Ubisch, G.: Der Erbgang der Dystrophia musculorum progressiva, *Deutsche Ztschr. f. Nervenhe.* **105**:276, 1928.

15. Manson, J. S.: Hereditary Myopathy—A Family Showing Dominant Transmission, *Brit. M. J.* **2**:1256, 1935.

unless the disability appears relatively late in life or progresses sufficiently slowly to permit some of the patients to marry and have offspring. These considerations probably explain the comparative infrequency of this type of transmission.

The data given in the table show that the type of hereditary transmission of muscular dystrophy could be established for only 40 of the 125 patients in this series. Possible explanations for occurrence of muscular dystrophy in the remaining 85 patients are as follows: (1) The cases were sporadic; (2) the disease was inherited by either a recessive or a dominant factor but was of abortive form in the parents or other members of the family and was unrecognized; (3) heredity was by a simple sex-linked recessive factor, but the fortuitous escape of other members of the family in recent generations prevents determination of the mechanism of inheritance; (4) inheritance was by multiple recessive factors. From the data available on these patients one can only postulate regarding these possibilities. The question whether or not any or all of the cases were of sporadic occurrence can be answered only after all other possibilities have been excluded.

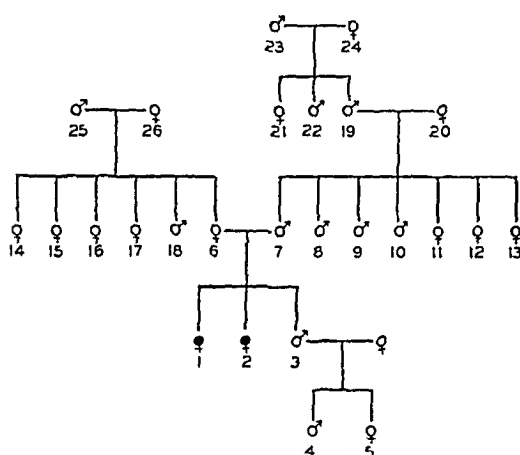


Figure 10

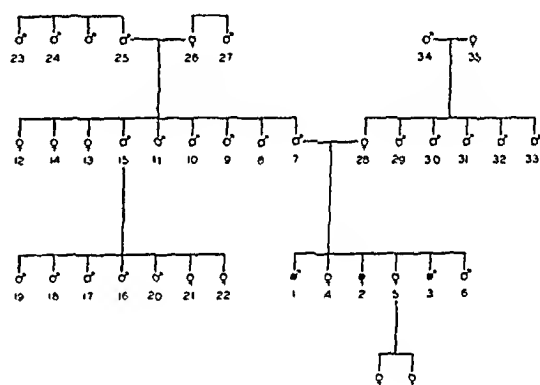


Figure 11

Fig. 10.—Family tree of 2 sisters with progressive muscular dystrophy. In patient 1, aged 29 years, with onset of symptoms at the age of 12 years, the condition is now far advanced. Patient 2, with onset of the disease at the age of 11 years, was totally incapacitated at the age of 27 years and died at the age of 33 years. Sibling 3, a normal male, is 35 years old and has 2 children—4, aged 4 months, and 5, aged 2 years. The mother of the patients (6) died at the age of 34 years, with edema. The father (7) and his siblings, 8 to 13 inclusive, are living and well at ages ranging from 55 to 68 years; each, except 7, has several children and grandchildren, who are free from muscular disease. Subject 14 died at the age of 25 years, of heart disease. Subjects 15 to 22 have died, but were free from muscular disease; all had children, all of whom were normal. Subjects 23 to 26 inclusive died at ages ranging from 75 to 99 years and were without muscular disease. The paternal grandfather (19) went south with the Union Army, married and settled in Maryland. Since then there have been frequent family reunions. Inquiries among collaterals of the family tree revealed no cases of muscular dystrophy other than those of patients 1 and 2.

Fig. 11.—In patient 1 the disability started at the age of 8 years and was moderately advanced at the age of 13 years. Patient 2 was always weak; the disease was moderately advanced at the age of 15 years. In patient 3 weakness was first noted at the age of 14 years, and he died when 18 years old. Siblings 4, 5 and 6, aged 18, 26 and 22 years respectively, are normal. The father (7) is 54 years old. His siblings 8 to 13, aged 47 to 65 years, have a total of 35 children, all of whom are normal. Subject 15 is his twin brother. The paternal grandfather (25) died at the age of 82 years; he was very strong and was said to have been able to carry a load of 400 pounds (181.4 Kg.) on his shoulders when he was 62 years old. The paternal grandmother (26) died at the age of 62 years. Subjects 29 to 33, the mother's siblings, had a total of 15 children, all of whom were normal. The maternal grandfather (34) died at the age of 82 years, and the maternal grandmother (35), at the age of 80 years.

Weitz¹⁶ expressed the belief that the disposition to the disease arises through mutation in both males and females. This disposition is believed further to be transmitted to half of the descendants and develops into the disease syndrome in the males, and only infrequently in the females. Weitz offered no explanation for the difference in incidence in the two sexes. Diehl, Hansen and von Ubisch¹⁷ rejected the postulation that muscular dystrophy arises by mutation. On the basis of the investigations of Morgan on mutations in *Drosophila*, these authors expressed the belief that mutations in human beings occur far too infrequently to account for the incidence of muscular dystrophy. Kostakow and Bodarwé¹⁸ referred the occurrence of muscular dystrophy to mutation of heredity factors derived from previous generations. The further inheritance was considered to be by dominant or recessive genes.

Dawidenkow and Kryschowa¹⁹ stated the opinion that muscular dystrophy is transmitted by a dominant factor. They examined the mothers of some patients and found minor structural changes which they concluded to be manifestations of dystrophy. These changes included kyphosis, large calves, flat feet, abdominal hernia, cyanosis of the hands and absence of the achilles reflex. It was postulated that the mothers of patients transmit the disease by a "retarded" dominant factor to 37 per cent of their offspring. While no effort was made in our studies to examine every living forebear of the patients, many were examined and were found to have structural changes of no greater frequency or severity than most persons in whose families dystrophy had never occurred. In our opinion, the validity of one's considering the minor changes described by Dawidenkow and Kryschowa as manifestations of dystrophy is open to serious question. While the postulation of these authors might be an adequate explanation for the occurrence of some "isolated" cases of muscular dystrophy, our observations suggest that most cases cannot be explained on this basis.

The third possibility, that of inheritance by a simple, sex-linked recessive factor, appears to be a mechanism more likely to operate in at least a proportion of the cases. Most of the studies on the heredity of this disease have dealt with material on relatively few generations. In most families, information regarding disease in more than a few generations is either lacking or of dubious value. Therefore, cases of muscular dystrophy can appear to be "isolated" or "sporadic" if other male members of the family in the present and recent generations have fortuitously received the healthy sex chromosome. More complete data might show that males in earlier generations had been affected and thus indicate the sex-linked character of the inheritance. A schematic presentation of this formulation is given in figure 12. It will be noted that 50 per cent of sons of heterozygous mothers could be expected to be affected by the disease, whereas all the sons of a homozygous mother would have the disease. Instances in which the mother could be considered as homozygous were not met with in this series. While the presence of the disease in all sons was seen in certain families, for example, those shown in figures 1 and 2, the mother to be homozygous must be the issue of a male affected with the disease and a female who has transmitted to her daughter a sex chromosome con-

16. Weitz, W.: Der Erbgang der Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenlh. **102**:209, 1928.

17. Diehl, F.; Hansen, K., and von Ubisch, G.: Der Erbgang der Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenlh. **99**:54, 1927.

18. Kostakow, S., and Bodarwé, K.: Gibt es einem einkeitlichen Erbgang bei der progressiven Muskeldystrophie? Deutsches Arch. f. klin. Med. **181**:611, 1938.

19. Dawidenkow, S., and Kryschowa, N.: Untersuchungen angeblich gesunder Verwandter von Muskeldystrophikern, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:31, 1930.

taining the gene for muscular dystrophy. None of the maternal grandfathers of our patients with a recessive type of inheritance had muscular dystrophy. The formulation that in some "isolated" cases of dystrophy the disease is inherited by a simple sex-linked recessive factor could account for the greater incidence of the disease in males.

The fourth possible explanation for the occurrence of "isolated" cases has already been considered by other workers. In fact, Dittrich²⁰ questioned whether progressive muscular dystrophy can ever be the result of a simple hereditary factor. He stated the belief that the assumption of multiple factors makes comprehensible the various types of the disease. Diehl, Hansen and von Ubisch¹⁷ postulated that

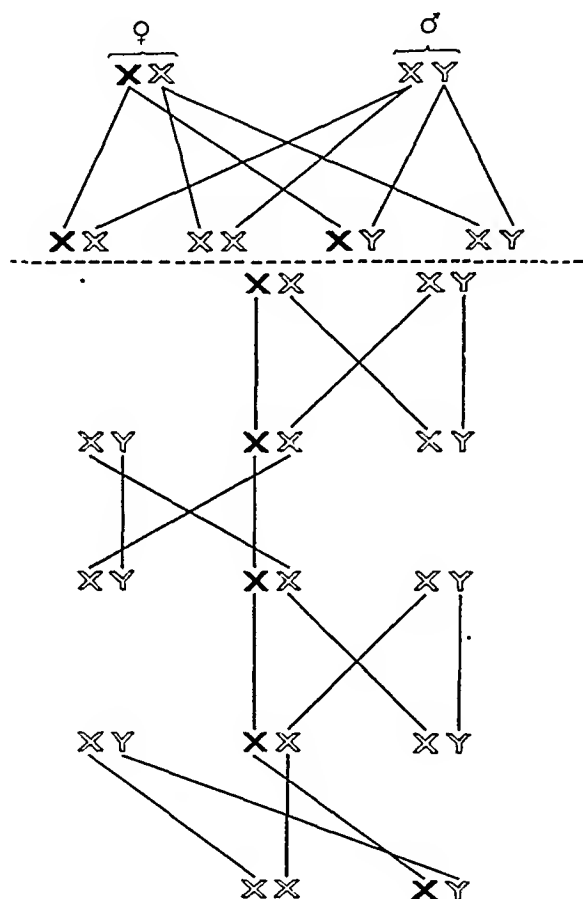


Fig. 12.—Schemas showing simple sex-linked recessive inheritance (based on Morgan [Morgan, T. H.: *The Physical Basis of Heredity*, Philadelphia, J. B. Lippincott Co., 1919]). The sex chromosome containing the factor for progressive muscular dystrophy is designed as a solid X. The normal sex chromosome is shown as X in outline. The schema above the dotted line shows transmission of the chromosome containing the disease factor to both males and females in the next generation. The schema below the line shows how male descendants can fortuitously escape the disease for several generations. Since heterozygous females possessing only an affected chromosome will not manifest the disease, the transmission of the chromosome with the factor for dystrophy to a male in the last generation will give rise to so-called isolated, or sporadic, cases of muscular dystrophy.

muscular dystrophy is dependent on two factors, which the authors designated as C and D. Normal persons were considered to have one of the factors (C or D) or neither. Persons with the disease were thought to have both C and D. The

20. Dittrich, R.: Zur Vererbung der progressiven Muskeldystrophie, *Verhandl. d. deutsch. orthop. Gesellsch.* (1931), 1932, Kong. 26, p. 69.

authors compared their scheme of heredity with that used for the inheritance of blood groups. They concluded that the scheme explains the occurrence of the disease in children of normal parents and the instances in which the transmission of the condition skips one or more generations. However, the scheme does not explain the difference in the number of persons of the two sexes who have muscular dystrophy. The authors expressed the belief that while the influence of sex might theoretically play a role, inheritance could be explained without consideration of sexual influences. Frequent mutations find no place in their scheme. Minkowski and Sidler²¹ reported an interesting family tree in which there were 8 males and 5 females who had muscular dystrophy. The family consisted of two branches, the forebears of which had lived in an isolated valley in Switzerland for many generations. There had been numerous intermarriages, and all parents of the patients were blood relatives. The appearance of muscular dystrophy in the families was abrupt, after a long period of intermarriage. Since the disease had been absent in all the forebears, Minkowski and Sidler concluded that its inheritance was of recessive nature. Moreover, the fact that the disease arose only among children of union of the two branches of the family suggested that heredity was by double recessive factors rather than by a single factor.

Multiple hereditary factors have often been described in breeding experiments on animals.²² Of special interest are the observations of Wood²³ on the inheritance of horns in sheep. Both sexes of the Suffolk sheep are hornless, whereas both sexes of the Dorset sheep are horned, although the horns of the ram are larger. Horned Dorset sheep crossed with hornless Suffolk sheep gave horned sons and hornless daughters. When these offspring were inbred, there were 3 horned males to 1 hornless male and 3 hornless females to 1 horned female. The results can be explained by the assumption that in the male one gene suffices to produce horns, whereas in the female two genes for horns are necessary to produce horns. Therefore in this instance the hereditary factor is sex-limited rather than sex-linked. Among mutants of *Drosophila melanogaster* several cases of sex-limited characters are found, the effect of a gene on one sex being greater than that on the other.²² The assumption of a similar mechanism in some cases of progressive muscular dystrophy would go far in explaining the high ratio of males to females (3:1) with this disease. Moreover, the formulation that fewer recessive hereditary factors are required for the development of muscular dystrophy in males than in females suggests the importance of the "sex hormones" on the incidence of this disease.

Macklin²⁴ expressed the opinion that the variation in modes of inheritance observed in different families could be explained on the assumption that similar clinical entities may be due to diverse pathologic conditions. Application of her formulation to progressive muscular dystrophy implies that among a group of patients with this disease the muscular symptoms are due to one type of process in some persons and to other types in others. In the absence of adequate data on the etiologic factors in muscular dystrophy, this question cannot be answered at present. It is known that certain diseases, such as exophthalmic goiter, can sometimes produce muscular disability that closely resembles muscular dystrophy.

21. Minkowski, M., and Sidler, A.: Zur Kenntnis der Dystrophia musculorum progressiva und ihren Vererbung, Schweiz. med. Wchnschr. 9:1005, 1928.

22. Morgan, T. H.; Sturtevant, A. H.; Muller, H. J., and Bridges, C. B.: The Mechanism of Mendelian Heredity, New York, Henry Holt & Co., 1923.

23. Wood, T. B.: Inheritance of Horns and Face Color in Sheep, J. Agric. Sc. 3:145, 1909.

24. Macklin, M. T.: The Role of Heredity in Disease, Medicine 14:1, 1935.

Askanazy²⁵ demonstrated considerable muscular involvement associated with exophthalmic goiter, but there could have been little difficulty encountered in making the diagnosis of thyroid disease in the cases reported by him. On the other hand, the 2 patients of Shorr, Richardson and Wolff²⁶ had muscular disability practically indistinguishable from that seen with progressive muscular dystrophy, and only with the aid of adequate laboratory investigations and a study of the effects of iodine could the diagnosis of exophthalmic goiter be established. Thyroidectomy in both cases induced almost complete restoration of muscular function. Studies of thyroid function were made in practically every case reported in the present series.

Consanguinity of Parents.—In only 1 family (fig. 9) were the parents of the same family stock. In this instance, the mother and father of the 2 patients were first cousins. Blood relationship of parents was stated by Minkowski and Sidler²¹ and by Mason and Meloy²⁷ to be of importance in the families reported on by them.

Relationship of Age of Patient When Symptoms Began and Clinical Course.—An attempt was made to determine the speed of progression of muscular disability and to relate this to the age of the patient when symptoms first were noted.

The amount of muscular disability was estimated by the following criteria:

Observed Limitation in Muscular Function	Estimated Muscular Disability, Per Cent
Slight weakness in arms or legs.....	10
Waddling gait	15
Arms cannot be raised above shoulder; support needed in arising from floor; patient ascends stairs moving one foot at a time.....	25
Arms cannot be raised above midthoracic line; patient "climbs up" on thighs in getting up from prone position; ascends stairs holding on to railing.....	40
Arms cannot be raised above level of waist; patient arises from floor only with great difficulty; stair climbing almost impossible; moderate scoliosis or lordosis	50
Patient unable to get up from sitting position; unable to climb stairs; unable to get up from floor.....	70
Patient unable to walk; unable to lift arms above level of waist.....	80
Patient unable to walk, turn over in bed or feed himself; advanced scoliosis or lordosis	90

It is recognized that these values probably do not represent the actual quantitative reduction in total muscular function of the patients. However, it is felt that they do represent the relative impairment of muscular function in the patients in this series and serve a useful purpose for comparison of the different subjects.

When the total muscular disability expressed as the percentage of reduction in muscular function was divided by the number of years during which symptoms had been present, a value representing the average yearly decrease in muscular function was obtained. In figure 13 the average yearly decrease in muscular function in 92 patients is shown in relation to the ages at which muscular symptoms began.

25. Askanazy, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii insbesondere über die dabei auftretende Muskelerkrankung, *Deutsches Arch. f. klin. Med.* **61**: 118, 1898.

26. Shorr, E.; Richardson, H. B., and Wolff, H. G.: Unpublished observations; patients presented before the Section of Medicine, New York Academy of Medicine, Dec. 17, 1940.

27. Mason, W. S., and Meloy, R. C.: Progressive Muscular Atrophy: Five Cases in One Family, *J. Oklahoma M. A.* **23**:265, 1930.

The data show that when the disease began in the first decade of life the clinical course was rapid; in most instances the average yearly loss in muscular function was 13 per cent. When the onset of symptoms appeared during the second decade, the progress of the disease was slower, the yearly loss in function averaging about 7 per cent, and when the onset was in the third decade the average progression in disability was only about 3 per cent per year. There were significant differences among the patients in most of the age groups: for example, in a patient in whom the symptoms began at the age of 7 years, the yearly increase in disability was only 5 per cent, whereas in another patient it was 18 per cent. The average value for the 10 patients in this age group was about 12 per cent. Therefore, while the data in this series can be used in a general way in the prognosis for a patient with muscular dystrophy, the prediction applies only to the average for the patients in the same group. These observations confirm the opinion stated by Gowers,¹ Voshell¹⁰

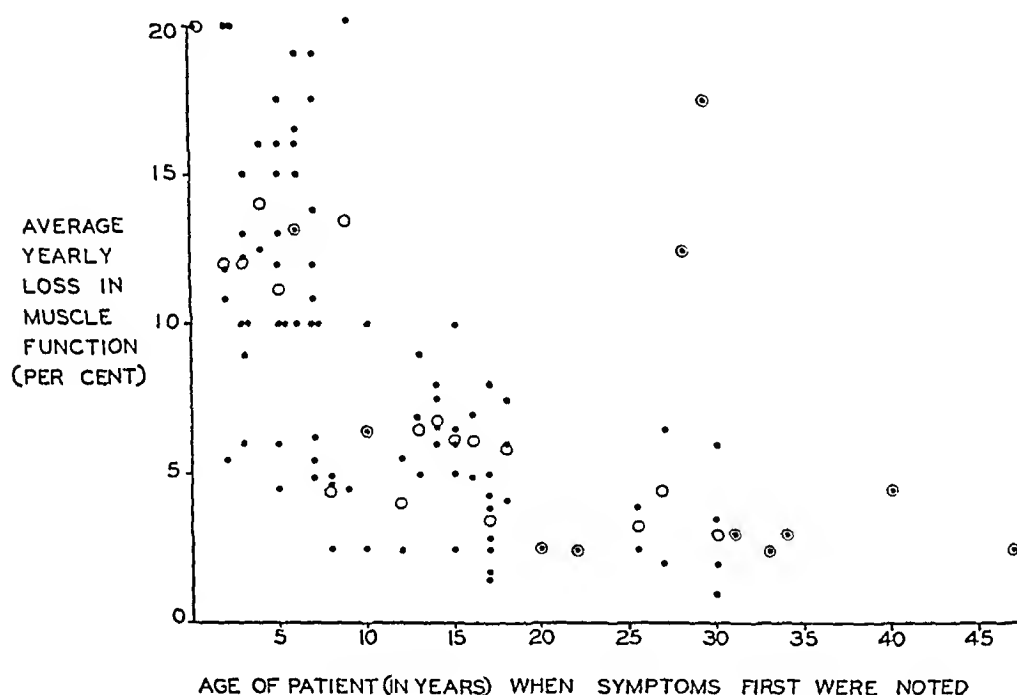


Fig. 13.—Relationship between progression of disability and age of patient when muscular symptoms first were noted, in 95 cases. The dots represent data on individual patients; the open circles, average values for the different age groups.

and Hurwitz³ that the earlier in life symptoms of muscular dystrophy develop the more rapid the progression of disability is likely to be.

It can also be stated that, in general, the age of onset of the disease was approximately the same in all patients in any one family, although this age of onset showed considerable variations among the different families. Moreover, the rapidity with which the muscular symptoms progressed was roughly similar in patients in the same family. Macklin²⁸ stated her belief that these phenomena apply to most hereditary diseases.

SUMMARY

The heredity of progressive muscular dystrophy was studied in 75 families, in which a total of 125 members were affected with the disease. On 85 of these

28. Macklin, M. T.: The Relation of the Mode of Inheritance to the Severity of an Inherited Disease, *Human Biol.* 4:69, 1932.

patients clinical and chemical studies were made, in most instances at frequent intervals over periods of several years. The observations were as follows:

1. Fifty-four per cent of the 125 patients gave a history of at least 1 other member of the family affected with the disease; of the 85 patients who were examined, 25 per cent gave a positive familial history of the disease.

2. More males had progressive muscular dystrophy than did females. The ratio of males to females was 3:1.

3. Twenty-six males inherited the disease by a simple sex-linked recessive factor; e. g., the muscular dystrophy appeared in the males but was transmitted by apparently healthy females.

4. In 7 males and 7 females transmission of the disease was by a dominant hereditary factor.

5. The exact mechanism of heredity in 61 males and 24 females was not determined, but was of a recessive type. The ratio of males to females in this group was 2.5:1. It is postulated that in this group inheritance in many instances was by a simple sex-linked recessive factor. The sex chromosome carrying the dystrophy factor probably was transmitted by the females of the family for a number of generations without transmission to a male other than the patient and his siblings. The fortuitous absence of the disease in the male members of previous generations on which information is available would mask this type of hereditary transmission. However, it is unlikely that this mechanism accounts entirely for the frequency of the disease among males. Another possible type of hereditary transmission is one of multiple recessive factors in which the number of factors necessary to induce the condition is fewer for males than for females. A similar influence of sex on the number of hereditary factors required for certain characteristics has been demonstrated in many species of animals. The influence of sex on the incidence of progressive muscular dystrophy might be of importance in the concept of the mechanism and cause of the condition.

6. There was a definite relation between the age of the patient when the symptoms first were noticed and the clinical course of the disease. In patients in whom the disease appeared early in life disability developed much faster than it did in patients in whom the first symptoms appeared at a later age.

7. In the present series, the patients whose inheritance of the disease was by a dominant hereditary factor manifested their first symptoms relatively late in life. In these patients the progress of the disease was slow, and investigations showed that the disease remained localized to certain muscle groups for long periods.

8. In contrast, when progressive muscular dystrophy developed early in life the process usually became extensive in distribution and involved most of the muscles early in the course of the disease.

525 East Sixty-Eighth Street.

STUDIES IN DISEASES OF MUSCLE

XIII. PROGRESSIVE MUSCULAR DYSTROPHY OF ATROPHIC DISTAL TYPE; REPORT ON A FAMILY; REPORT OF AUTOPSY

A. T. MILHORAT, M.D.

AND

H. G. WOLFF, M.D.

NEW YORK

In the preceding report in this series¹ reference was made to a family in which 12 members had progressive muscular dystrophy with inheritance by a single dominant hereditary factor. The data on heredity were illustrated in figure 7 of that report.

The symptoms, clinical observations and changes in creatine metabolism, as well as the inheritance of the disease in members of this family, were so unusual for progressive muscular dystrophy that a presentation of case histories appears desirable. In many respects the clinical picture resembled that of Charcot-Marie peroneal muscular atrophy, in which transmission of the disease usually is by a dominant hereditary factor.² Since this family contained 12 of the 14 patients in the entire series in whom inheritance was by a dominant factor, it seemed of importance to the general problem of muscular disease, especially the heredity of progressive muscular dystrophy, to determine whether these patients had muscular dystrophy or whether the muscular disease was peroneal muscular atrophy. Most of the patients were followed for a period of seven years. During this entire time, it was impossible to be certain of the diagnosis until a complete necropsy was made in 1 case.

Six cases, with the observation at autopsy in 1 of them, are reported. The numbers assigned to the cases are those used in the family tree in the previous report.¹

REPORT OF CASES

CASE 3.—*History.*—The patient was not examined by us. She was hospitalized at the Montefiore Hospital, New York, from July 10 to Nov. 10, 1923. The director of the hospital supplied the following information: A housewife aged 38 was admitted on July 10, 1923, complaining of weakness of the lower extremities and difficulty in walking. Her illness began ten years before her admission, when she first noted pain and a feeling of tiredness in both thighs and legs. Her legs gradually became weaker, and she tired excessively on walking. Later she noted difficulty in raising the legs and had to "pick them up with her hands and place them on a chair" when attempting to put on her stockings or shoes. She soon noted difficulty in arising from the floor when she was scrubbing unless she assisted herself by firmly grasping surrounding objects. Her walking became progressively more difficult and unsteady up to the time of admission.

The past history was noncontributory.

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From the Departments of Medicine and Psychiatry, Cornell University Medical College; the Russell Sage Institute of Pathology, and the New York Hospital.

1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: XII. Heredity of Progressive Muscular Dystrophy; Relationship Between Age at Onset of Symptoms and Clinical Course, Arch. Neurol. & Psychiat., this issue, p. 641.

2. Small, S. M., and Milhorat, A. T.: Studies in Diseases of Muscle: VI. Progressive Peroneal Muscular Atrophy; Report on a Family, with Study of Heredity and Metabolism of Creatine and Creatinine, Arch. Neurol. & Psychiat. 40:911 (Nov.) 1938.

Examination.—The patient was a middle aged woman, who appeared fairly well nourished. She walked with a waddling gait, with abdomen thrown forward and compensatory lordosis. In rising from a recumbent position she supported herself by placing her hands on her knees. The left pupil was slightly larger than the right, but both reacted to light and in attempts at her near vision. Motor power in the upper extremities appeared to be normal. The tendon reflexes in the upper extremities were hyperactive and equal on the two sides. There were no pathologic reflexes. The biceps and deltoid muscles appeared to be slightly underdeveloped. As compared with the thighs both legs appeared smaller than normal, and the wasting was more pronounced in the muscles below the knees. The left calf measured $11\frac{3}{4}$ inches (29.9 cm.) in circumference and the right calf $11\frac{1}{2}$ inches (29.2 cm.). There was atrophy of the muscles of the thighs. The circumference of the right thigh was $14\frac{1}{2}$ inches (36.8 cm.) and that of the left 15 inches (38.1 cm.). Weakness was moderate in the hamstring group of muscles on the left side and slight on the right. Foot drop, with inversion of the left foot, was present bilaterally. The patient could move the toes. The only reflex obtained in the lower extremities was the patellar, which was sluggish bilaterally, but a little more active on the left side. The abdominal reflexes were present. No fibrillations were observed. There were no sensory defects. The Wassermann reaction of the blood was negative. Roentgenograms of the spine and skull showed nothing abnormal.

The diagnosis was progressive muscular dystrophy (atrophic type).

Subsequent Course.—The muscular disability progressed steadily, and the patient died in 1934, at the age of 49 years.

CASE 5.—History.—A widow aged 67 had extensive muscular wasting of many years' duration. She stated that at about the age of 43 she first noted weakness of the feet. The symptom was insidious in onset and was slowly progressive. A few years later the muscles of the hands and calves were affected. The process in the upper extremities gradually extended to the muscles about the shoulders. There was no pain or paresthesia. She was seen on Feb. 19, 1934, when the results of examination were about the same as those obtained on Jan. 22, 1941, to be described, except that muscular wasting was not as advanced and she was able to walk with assistance. In 1936 the patient tripped and fell, sustaining a fracture of the lower end of the femur. This necessitated a prolonged period of rest in bed, and thereafter she was unable to walk again.

Examination (Jan. 22, 1941).—The patient sat comfortably in bed but was unable to raise the arms more than a few inches from the side of the body. The pupils were equal and regular and reacted normally to light, but there was little reaction in attempts at near vision. The movements of the eyeballs were limited in attempts at convergence; otherwise, the extraocular movements were normal. Examination of the fundi showed the disks to be normal, but there was considerable sclerosis of the retinal arteries. There was no weakness of the face. The tongue showed no wasting or fibrillations. Gross power of all the muscles of the upper extremities was greatly reduced. The patient was able to exert little resistance to passive flexion or extension of the upper extremities. She could lift the arms only a few inches from the side of the body. Muscular wasting was moderate in the upper portions of the arms, more definite in the forearms and fairly advanced in the hands. There was atrophy of the thenar and hypothenar eminences and of the intrinsic muscles of the hands. The grip was weak, and approximation of the thumb and index finger was feeble. The hand presented a moderately advanced main en griffe appearance. The finger nails had numerous ridges extending the length of the surfaces. The patient stated that this condition had been present for about five years. There was slight wasting of the muscles about the shoulders, but no definite flaring of the scapulas could be seen. The lower extremities were very weak, and the patient was practically unable to make any movements with them. There was a definite bilateral foot drop, and the feet could not be brought from this position even when considerable force was applied by the examiner. The patient was unable to move the toes. The feet were flat and wasted. There was considerable weakness of the thighs, and the lower extremities could be flexed or extended at the hip without much difficulty by the examiner even when the patient exerted all possible power. The muscles of the peroneal and tibial groups appeared to be of normal size. They had a rather hard feel, with a doughy character. The skin over the hands and feet was smooth and shiny. The tendon reflexes in the upper extremities were active; in fact, they suggested some hyperactivity, but there was no finger stretch reflex. The patellar and achilles reflexes were absent. The plantar response was flexor in type. There was moderate diminution in vibration sense over the toes of both feet. Sensibility for pain, light touch and position was normal. There were no fibrillations.

The patient experienced considerable dyspnea and weakness when she attempted to sit up with her feet hanging over the side of the bed. After the feet had hung for an hour or so, definite edema of the ankles developed. The heart was enlarged; the rate was rapid, and there were numerous premature contractions. The picture was one of arteriosclerotic heart disease.

Formulation.—Examination at this time showed essentially the same condition as that noted seven years previously. There had been little progression in the muscular disability except that occurring subsequent to the fracture of the leg and the prolonged rest in bed necessitated by treatment of the fracture. The foot drop and the contractures of the feet probably were due to prolonged inactivity and the weight of the bedclothes on the feet.

Subsequent Course.—During the last week of November 1941 pain developed in the abdomen. This pain came on acutely, was rather severe and persisted for a few days. The patient then continued in about the same condition as prior to this episode. About December 13 she had

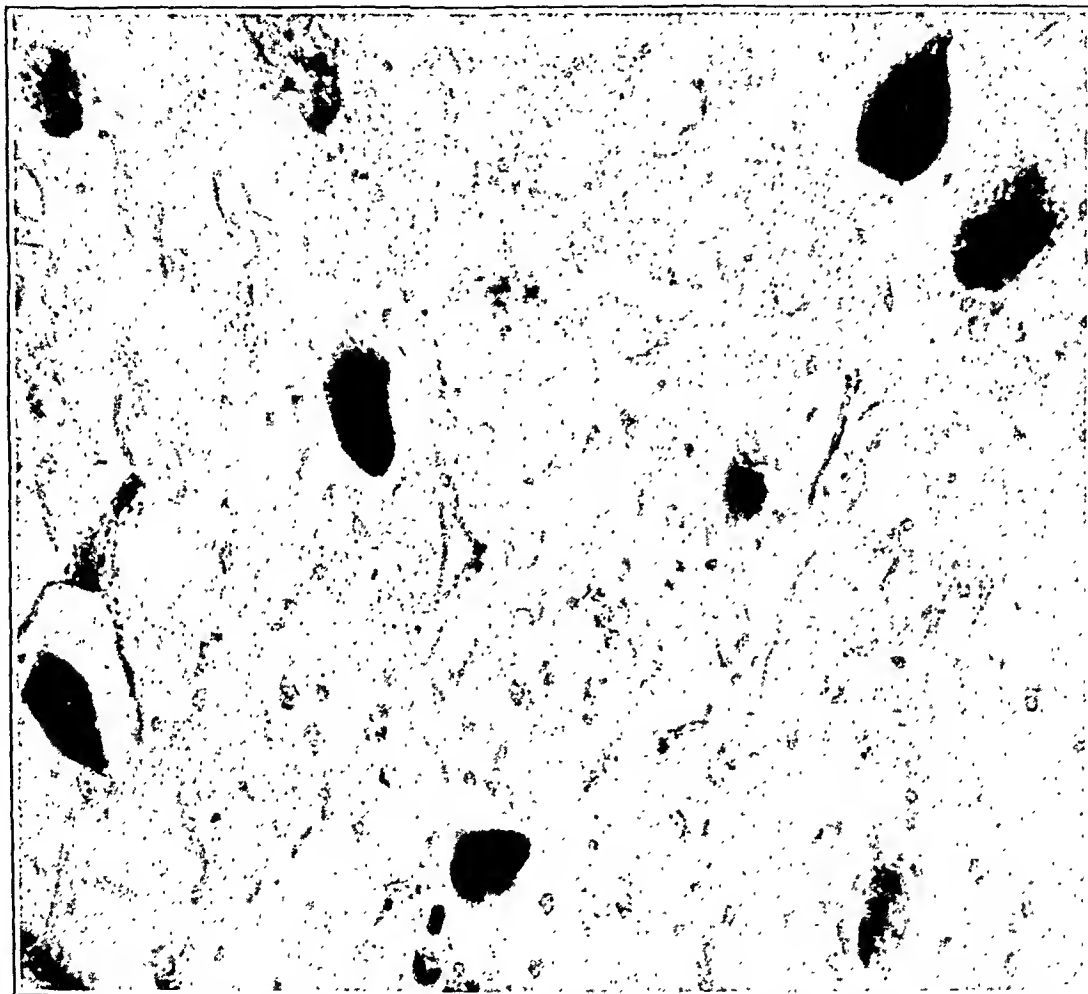


Fig. 1 (case 5).—Motor ganglion cells of the anterior horn, midcervical level (description in text).

a recurrence of abdominal pain, which came on acutely, was very severe and persisted. The patient gradually became comatose and died on Dec. 20, 1941.

Autopsy, by Dr. L. D. Stevenson and Dr. D. P. McEndy, of the department of pathology, was performed twelve hours after death.

Gross Examination.—*Inspection:* The body was that of a white woman, which measured 152 cm. in total length and weighed 48 Kg. It was poorly developed but moderately well nourished. There was only a slight amount of rigor mortis of the upper extremities; none was observed in the lower extremities or the neck. There was considerable loss of subcutaneous fat, particularly in the upper extremities. The muscle tissue about the shoulder girdle and the upper and lower portions of the arms was slight in amount, soft and flabby. The supraspinatus and infraspinatus muscles were almost completely absent. The spines of the scapulas were conspicuous throughout their entire length, and the bodies of the scapulas could easily be palpated. The muscles of the flexor surfaces of the forearms were considerably

decreased in size. The fingers and hands were held in a semiextended position. No rigor mortis was observed in the fingers, but they tended to assume a perfectly straight plane. The general outlines of the lower extremities and of the pelvis were within normal limits. No such atrophic picture as was seen in the upper extremities was present here. There was moderate edema of the legs, ankles and feet. The feet were plantar flexed and everted outward. The skin over the anterior surface of the legs was thin and shiny, and there was a mottled pink discoloration of the skin in these regions and over the anterior surfaces of the thighs. The thigh muscles were soft and flabby, but not to an extent comparable to that observed in the upper extremities.

Muscles: The muscles of the body that were examined were smaller than normal and paler than is usually seen. This was noted particularly in the rectus abdominis muscles and in the muscles of the neck and shoulders. Those of the upper portions of the arms were observed to be in a similar condition, but less pale.

Brain and Spinal Cord: The skull was thick, and irregularly so. Neither the pachymeninges nor the leptomeninges showed change. The venous sinuses were patent. The cranial nerves and the pituitary were not remarkable. Nothing unusual was noted in examination of the accessory nasal sinuses or of the middle and internal ears.

The vessels of the circle of Willis were moderately sclerotic. There were two small whitish nodules on the under surface of the dura of the upper parietal region on the left side. One measured approximately 1 cm. and the other approximately 0.5 cm. in diameter. Both were rather flat. There was fairly extreme cortical atrophy of both hemispheres, particularly in the frontal and parietal regions and to a lesser extent in the temporal region. No evidence of internal hydrocephalus was noted. There was no softening or hemorrhage into the brain substance. No lesion was visible in the basal ganglia or in the internal capsule.

An area of flattening, possibly an artefact (?), was present in the upper thoracic region of the spinal cord, just below the cervical region. There was considerable congestion of the capillaries of the gray matter of the thoracic and lumbar regions of the cord.

Microscopic Examination.—**Muscle:** A section taken through the rectus abdominis muscle showed this tissue to be almost completely replaced by fat. The few strands of muscle that remained stained very lightly, but their cross striations persisted. Between the muscle fibers in some places were collections of cells with dark, round and spindle-shaped nuclei.

Only small collections of fat were seen in a section taken from the biceps muscle, but the muscle fibers took a very pale stain. The cross striation remained. A similar, but less extreme, picture was seen in a section through the psoas muscle. Here the fibers were scanty, and considerable fat was seen between them in some places.

Brain and Spinal Cord: A section of the precentral gyrus stained by the Nissl method showed that the Betz cells were well preserved and the other cortical layers normal in appearance, although there was slight dropping out of cells. A section of the spinal cord in the midcervical region showed no loss of myelin. The anterior horn cells were normal in number, but they gave evidence of atrophy, with tortuous processes and deeply staining cytoplasm (fig. 1). In a similar section through the upper thoracic region the nerve cells of the anterior horns presented the same appearance. In the upper lumbar region pyknosis of the anterior horn cells and other atrophic changes were apparent. In the sacral region the condition of the anterior horn cells was similar. It is likely that these changes in the anterior horn cells throughout the spinal cord were the result, rather than the cause, of muscular disease. A section of the right femoral nerve stained for fat showed no degenerative change.

Additional Autopsy Observations: There were multiple healed infarcts of the spleen and kidneys; embolism of the abdominal aorta and iliac, superior mesenteric and celiac arteries; massive infarction of the terminal portion of the jejunum and of the proximal half of the ileum; serofibrinous peritonitis; bilateral hydrothorax; partial atelectasis of the lower lobes of both lungs; passive congestion of the liver, with fatty degeneration and beginning cirrhosis; advanced arteriosclerosis of the thoracic and abdominal portions of the aorta; moderate arteriosclerosis of the cerebral, coronary, mesenteric, splenic and common iliac arteries; slight fibrosis of the myocardium; fibrous pleural adhesions at the apex of the left lung; calcified nodules in the lower lobe of the left lung and in corresponding peribronchial lymph nodes; small cysts of both kidneys; hemangioma of the spleen, and mucus cysts of the fundus of the uterus.

CASE 8.—History.—A housewife aged 38 was first seen in the clinic on Nov. 16, 1934, with the complaint of difficulty in walking, of one year's duration. The patient stated that up to the age of 28 years she had no difficulty whatever in walking, but thereafter there was a gradually increasing sense of heaviness in the feet. This symptom was mild until about one year prior to her admission to the outpatient department, when it increased definitely. She found it necessary to be careful while walking, since she showed an increasing tendency to trip.

Examination and Clinical Course.—Examination showed the gait to be somewhat steppage in type, but there was no lordosis or other abnormality. Examination of motility showed no

abnormality except in the muscles below the knees. The calves were somewhat large and of wooden consistency. The feet were held moderately overextended. Extension of the feet appeared to be only slightly impaired, whereas flexion of the feet was weak. The tendon reflexes were active and equal on the two sides except for the ankle jerks, which were definitely reduced. Sensory function was normal. The patient weighed 69 Kg.

In July 1935 the patient visited another hospital, where a lumbar puncture was performed. After this procedure headache developed, and it was necessary for her to remain in bed about four weeks. During her prolonged period of inactivity the weakness of the feet progressed rather rapidly, and for the next three months she complained of pain in both feet whenever she walked. With the help of physical therapy the condition gradually improved and by the end of another month was about the same as before the lumbar puncture.

Subsequent Course.—During the next six years the condition of the patient was slowly progressive.

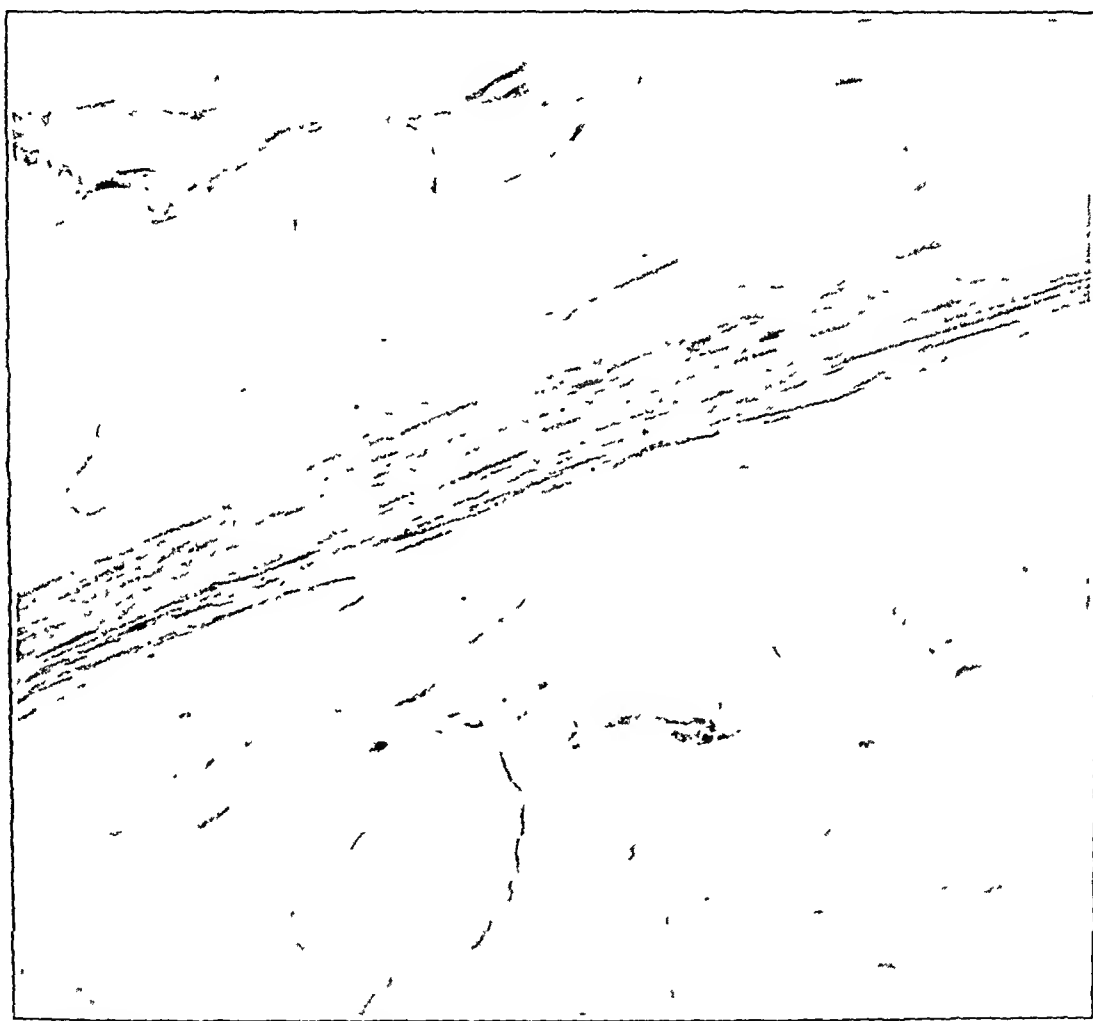


Fig. 2 (case 10).—Muscle removed post mortem from thigh (description in text).

CASE 10.—History.—A man aged 38 was first observed at the New York Hospital on Dec. 9, 1933. In 1926, at the age of 30, he began to have difficulty in raising his thighs. This gradually became worse, and in 1929 he had difficulty in extending his feet. In 1932 he was seen in another hospital, where a diagnosis of progressive muscular dystrophy was made.

Examination.—There was weakness of the iliopsoas muscles and of the lower extremities. The peroneal muscles were weak, although the calves were large. The muscles of the left calf were of wooden consistency. There was no definite wasting of the muscles of the upper extremities, but the left biceps muscle was weak and there was slight winging of the scapulas. There was no sensory defect. The patient weighed 79 Kg.

Clinical Course.—The muscular weakness and wasting gradually increased. Twelve years after the onset of the disability the patient had considerable difficulty in getting about. In 1938 he fell and sustained a fracture of the shaft of the femur. The fracture healed in normal manner, but thereafter the patient was unable to walk. In December 1939 pneumonia developed, and he died.

Examination of Muscle.—A piece of muscle removed post mortem from the right thigh by Dr. Ben Klotz was sent to us for examination. The report of the microscopic examination by Dr. N. C. Foot, of the department of surgical pathology, follows:

"Microscopic examination of the muscle tissue revealed the most profound changes yet seen in this laboratory. The main bulk of the tissue was rather normal-appearing fat, and one would not have suspected that muscle had been present until several strands of fibrous tissue containing much degenerated, but quite definite, striated muscle were encountered. In some portions these remains of striated muscle took a greenish color rather than the hematoxylin stain, indicating a changed reaction. These strands were short and faded into the fibrous tissue (fig. 2). Apparently, the sarcolemma cells remained somewhat longer than the other constituents. At various points there were small collections of lymphocytes, usually strung out in single or double file, paralleling the muscle strands. Dilated vessels were seen here and there.

"The diagnosis was progressive muscle dystrophy, terminal stage."



Fig. 3 (case 11).—Wasting of muscles below the knees. These changes were typical of all patients in this family during the moderately early stages of the disease.

CASE 11.—History.—A man aged 37, a theatrical agent, complained of difficulty in walking. About four years prior to his admission to the hospital, on Jan. 19, 1939, he noted that his feet made a slapping sound when he walked. This was noticed also by his friends, who frequently called his attention to it. About two years after the onset of this symptom the patient began to stumble over low objects, such as irregularities in the pavement, and on several occasions he fell. For about one and one-half years prior to his admission he noted a gradual increase in weakness of the calves and thighs. He was able to walk for only short distances and had to hold on the railing with his hands while ascending stairs. For one year he had cramplike pains in the left foot, and on occasion this foot felt numb. The patient stated the belief that the muscular weakness had been limited to the legs.

Examination.—The patient lifted his feet high while walking and brought them to the floor with a loud slapping sound. When the lower end of the tibia was grasped and the leg shaken, the foot seemed to be only loosely attached. The feet were kept in an overextended position, and the patient was unable to flex them. There were definite wasting of all muscles below the knee and slight weakness, but no wasting, of the muscles of the thighs (fig. 3).

The tendon reflexes were normal except that the knee and ankle jerks on the left side were slightly diminished. Sensory function was unimpaired.

Subsequent Course.—The patient was seen at frequent intervals during the next two and one-half years. During this period there was only slight increase in disability.

CASE 12.—History.—A male clerk aged 30 was first seen in the clinic on Jan. 16, 1939. He stated that for a few months he had noticed slight difficulty in walking, with a tendency to stumble over low objects. The symptoms had been mild, but the patient consulted a physician because his brother had had increasing difficulty in walking and the patient was apprehensive that he might be acquiring the same condition.

Examination.—At the time of the first visit to the clinic examination disclosed no evidence of muscular disease. The patient was seen again in May 1940, with a history that the difficulty in walking had increased slowly but progressively. At that time there was slight atrophy of the muscles of the calves and feet. There was no involvement of the muscles elsewhere. Sensory function was normal.

Subsequent Course.—The patient was seen on numerous occasions, and during the past year muscular disability had progressed slowly. At the time of writing the patient raised his feet rather high while walking and brought them to the floor with a slapping sound. There was definite weakness in flexion of the feet. The muscles of both feet and calves showed moderate wasting, somewhat more definite on the left side.

In August 1942 definite enlargement of the left calf was observed. Apparently, this change had occurred rather suddenly. The appearance and consistency of the calf had many characteristics of pseudohypertrophy, but the slight pitting produced by pressure in the lower portions of the calf suggested that the change in size was due to edema.

CASES 1, 2, 4, 6, 7 and 9.—The patients were not examined by us. Information obtained from other members of the family included the following data:

Patient 1, the earliest male in the family on whom data could be ascertained, had weakness and wasting of the muscles of the legs and feet but was able to walk until the time of his death, at the age of 55 years.

In patient 2 symptoms first were noted in the legs at the age of 26 years. The disability progressed steadily, and the shoulders were affected a few years later. The patient was incapacitated when she was about 35 years old, and she died at the age of 45.

Patient 4 had muscular disability similar to that of patient 3. Onset was at the age of 30 years. At the age of 35 she was incapacitated, and at the age of 45 she died.

Patients 6, 7 and 9 first noted symptoms in the legs and feet at the ages of 38, 28 and 28 years respectively.

METABOLISM OF CREATINE AND CREATININE

The metabolism of creatine and creatinine was studied in 4 of the patients by the methods described previously.³ In 3 of the patients the output of creatinine was reduced only moderately and in proportion to the reduction in muscular mass; spontaneous creatinuria was minimal, and the creatine tolerance was essentially normal. These results are similar to those observed in patients with wasting limited to relatively few muscle groups, such as muscular wasting subsequent to disease of the nervous system.⁴ In the family with progressive peroneal muscular atrophy reported by Small and Milhorat² the changes in the metabolism of creatine and creatinine were identical with those in the present 3 patients. However, in 1 patient (case 10), a man weighing 79 Kg., the daily output of creatinine was only 0.858 Gm. and the spontaneous output of creatine was 0.200 Gm. daily. These results are similar to those obtained for patients with widespread muscular involvement.

The essential facts regarding this syndrome can be summarized as follows: The onset occurs relatively late in life, usually about the end of the third decade.

3. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, *Arch. Neurol. & Psychiat.* **38**: 992 (Nov.) 1937.

4. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, *Arch. Neurol. & Psychiat.* **40**:663 (Oct.) 1938.

The muscles earliest and most severely involved are those of the peroneal and tibial groups. Progression of disability usually is slow; occasionally, after a period of a few years the muscles of the shoulder girdle or the hands are involved. Sensory defects and fasciculations are absent. The tendon reflexes are reduced or absent. In 2 instances enlargement of the calves suggested pseudohypertrophy; in another case one calf was increased in volume, as a result of edema.

Microscopic examination of muscles in 2 cases of advanced dystrophy showed almost complete replacement of muscle fiber by fat, with preservation of cross striations in the few remaining muscle fibers. In 1 case studied at autopsy microscopic examination of the spinal cord at different levels showed that the anterior horn cells were normal in number but had undergone atrophic changes, which were interpreted as being the result, rather than the cause, of muscular disease. No microscopic changes in the peripheral nerves were seen.

Cases of muscular dystrophy with involvement primarily of the distal muscles were reported by Gowers, Spiller, Batten, Oransky, Barnes and others. Gowers⁵ described a distal form of muscular dystrophy in 2 cases. In his first case, that of a youth aged 18 years, with a negative familial history for the disease, onset of symptoms was at the age of 12. The affected muscles were those of the lower portions of the legs and the hands, forearms and face. The calves were sufficiently large to suggest pseudohypertrophy. In Gowers' second case, that of a woman aged 23, symptoms began at 16. Three sisters were similarly affected, but no other instance in the family could be found. The muscles of the shoulder girdle and the entire upper extremities, including the hands, were wasted. In the lower extremities wasting was limited to the muscles below the knees. Gowers pointed out that in both cases the involvement of the legs was purely distal.

In Spiller's⁶ case, that of a man aged 50, symptoms had started thirty-five years previously with pains in the legs and feet. The patient noted no weakness until the age of 35 years, when the legs were observed to be getting thinner and somewhat deformed. Ten years later wasting of the muscles of the forearms and hands was noted. Muscular wasting progressed steadily but remained limited to the portions distal to the knees and elbows. The patient was unable to work after the age of 50 years. Sensory function was normal.

Batten⁷ reported cases which he called instances of a distal type of muscular dystrophy. In his first case, that of a youth aged 18, wasting of the muscles of the forearms, legs and thighs was present. In his second report Batten described a family in which muscular atrophy was limited to the portions below the knees. He emphasized the difficulty of distinguishing cases of this type from those of muscular atrophy of the peroneal type.

Oransky⁸ described an unusual form of muscular dystrophy in which the muscles of the shoulder girdle and peroneal groups were wasted. In some instances the muscles of the hands and the distal portions of the thighs were affected. Sensory function was normal. The disease began at the age of 18 to 20 years, and the course was slowly progressive. Six males and 4 females in four generations were affected. Heredity was by a dominant factor.

5. Gowers, W. R.: A Lecture on Myopathy and a Distal Form, *Brit. M. J.* **2**:89, 1902.

6. Spiller, W. G.: Myopathy of the Distal Type and Its Relation to the Neural Form of Muscular Atrophy (Charcot-Marie-Tooth Type), *J. Nerv. & Ment. Dis.* **34**:14, 1907.

7. Batten, F. E.: Distal Type of Myopathy, *Proc. Roy. Soc. Med.* **3**:92, 1909-1910; Distal Type of Myopathy in Several Members of a Family, *ibid.* **3**:93, 1909-1910.

8. Oransky, W.: Ueber einen hereditären Typus progressiver Muskeldystrophie, *Deutsche Ztschr. f. Nervenph.* **99**:147, 1927.

Dawidenkow⁹ observed a syndrome characterized by muscular atrophy of the Charcot-Marie type in the lower extremities and by wasting of the muscles of the shoulder girdle and the proximal muscles of the upper extremities. Several of the patients had thick fleshy lips similar to the condition seen in muscular dystrophy. In addition to his own cases, he collected several from the literature, including those of Oransky, which he concluded belonged to the same category. In Dawidenkow's cases there was hypesthesia of distal distribution in all four extremities, and heredity was by a dominant factor.

In the family reported by Barnes¹⁰ muscular atrophy was limited to the distal portions of the upper extremities. Moreover, the hypertrophy and pseudohypertrophy that preceded the atrophy make it exceedingly unlikely that the condition was identical with that seen in our patients.

Hoffmann and Clauss¹¹ reported observations on an interesting family in which 8 members, in three generations, were affected with muscular disability that resembled a combination of dystrophy and progressive spinal muscular atrophy of the Duchenne-Aran type.

Rimbaud and Giraud¹² described the cases of 3 brothers presenting a distal type of muscular dystrophy with onset at about puberty. The early development of contractures sharply distinguishes these cases from ours, in which no contractures occurred, except in case 5, in which the contractures developed as a result of prolonged inactivity. On the other hand, the cases described by Gowers and Oransky in many ways resembled those in the present report.

The observations at autopsy were more typical of those of progressive muscular dystrophy than of Charcot-Marie muscular atrophy, peripheral polyneuritis or progressive spinal muscular atrophy. Whereas the spinal cord is often entirely normal in cases of progressive muscular dystrophy (Middleton,¹³ Schultze,¹⁴ Landouzy and Dejerine,¹⁵ Spiller⁶ and Friesz¹⁶), slight or moderate changes, particularly in the ganglion cells of the anterior horns, have been reported by many observers.

Alterations in the ganglion cells of the anterior horns in the nature of degenerative changes or diminution in the number of motor cells were reported by Erb and Schultze,¹⁷ Pekelharing,¹⁸ Gibney,¹⁹ Frohmaier,²⁰ Lorenz,²¹ Foix and Nicolesco,²²

9. Dawidenkow, S.: Ueber die scapulo-peroneale Amyotrophie. (Die Familie "Z"). Ztschr. f. d. ges. Neurol. u. Psychiat. **122**:628, 1929; Scapulo-peroneal Amyotrophy, Arch. Neurol. & Psychiat. **41**:694 (April) 1939.

10. Barnes, S.: A Myopathic Family, with Hypertrophic, Pseudohypertrophic, Atrophic and Terminal (Distal in Upper Extremities) Stages, Brain **55**:1, 1932.

11. Hoffmann, H., and Clauss, O.: Klinischer und erbbiologischer Beitrag zur Lehre von der Muskeldystrophie (Kombination von Erbscher Dystrophie mit spinaler progressiver Muskelatrophie), Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:312, 1926.

12. Rimbaud, L., and Giraud, G.: Myopathie familiale du type péronier ou distal, Rev. neurol. **28**:1004, 1921.

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Poinso and Poursines²³ and others. In the case reported by Ballet and Laignel-Lavastine²⁴ muscular disability had been present about twenty years; at autopsy the motor cells of the anterior horns showed simple atrophy and considerable diminution in number. In the case reported by us the comparatively minor changes in the anterior horn cells can be interpreted as the result of muscular atrophy of long duration; certainly, they appeared insufficient to account for the advanced muscular wasting.

In brief, it can be stated that whereas the nature of the lesion in progressive muscular dystrophy is not known, the condition can be regarded as primarily affecting the muscles. However, in certain cases, especially those in which the muscular wasting has been of long standing, slight or moderate changes in the spinal cord are observed which are interpreted as being the result, rather than the cause, of the muscular atrophy. The alterations in our case, interpreted in the light of this formulation, are considered to be those of progressive dystrophy.

SUMMARY

A family in which progressive muscular dystrophy of atrophic distal type developed in 12 members is reported. The onset of symptoms usually was at about the age of 33 years (from 28 to 43 years). The muscles earliest and most severely affected were those of the legs and feet. Heredity was by a dominant factor. Autopsy observations in 1 case were similar to those often made in cases of progressive muscular dystrophy.

525 East Sixty-Eighth Street.

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EXPERIENCES WITH INTRAMEDULLARY TRACTOTOMY

II. IMMEDIATE AND LATE NEUROLOGIC COMPLICATIONS

LAURENCE M. WEINBERGER, M.D.

CHICAGO

AND

FRANCIS C. GRANT, M.D.

PHILADELPHIA

In 1938 Sjöqvist,¹ Stockholm, Sweden, described a new operative procedure for the relief of facial pain which was based on, and took advantage of, the peculiar anatomic and physiologic features of the intramedullary fibers of the trigeminal nerve. Briefly, the method involves the making of an incision into the lateral aspect of the medulla oblongata, about 3.5 mm. deep and 3.5 mm. long, and so placed as to transect the descending tract and spinal nucleus of the trigeminal nerve. In this way, half of the face is rendered analgetic and thermanesthetic, since the fibers for pain and temperature sense course in the descending tract. Tactile sensation, however, is not grossly disturbed because practically all the fibers conveying touch sensation terminate immediately in the main sensory nucleus of the trigeminal nerve, after entry of the nerve into the brain stem.

The introduction into neurosurgical practice of such an unusual innovation as an operation on the medulla oblongata carries with it the obligation of describing and appraising the neurologic sequels which might be imagined to follow an incision into so vulnerable a structure. Little information, however, has been published concerning these complications, possibly because attention and interest have been focused on the sensory alterations produced by the operation and on the clinical results obtained.

In his monograph,² which included the case histories of 9 patients on whom intramedullary tractotomy was performed, Sjöqvist stated: "No definite signs indicating a lesion to the dorsal nuclei were seen in the postoperative course of any case." Again, later, "No symptoms of dizziness or hemiataxia which might be interpreted as signs of lesion to the restiform body were seen." Perusal of his protocols, however, offers evidence to the contrary. In his case 9, he remarked that after operation the patient's gait "was more markedly staggering than upon admission." In his case 4, the patient "noticed some feeling of numbness of . . . the right side of his body (except the arm)," which Sjöqvist was inclined to believe was caused by the operation.

Other investigators have had similar experiences but, again, have glossed over, or at least have failed to emphasize, these neurologic complications. In 1 of the 3 patients operated on by Rowbottom,³ there were "a wild ataxia of the homolateral arm" and mild ataxia of the leg. These sequelae were said to have dis-

From the Neurosurgical Service and Laboratory of the Hospital of the University of Pennsylvania.

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appeared in three days. In a case in which Jackson operated but which Smyth⁴ reported, no disturbances appeared to follow operation immediately. However, when the patient was out of bed, two weeks later, pronounced disturbances in gait were observed. It was not stated whether or when these disappeared. On the other hand, Jackson and Ironside⁵ stated that there were no postoperative neurologic difficulties in the case in which they operated. Walker,⁶ with experience in 2 cases, briefly stated that the postoperative course was uneventful.

We⁷ previously reported in detail the nature of the sensory alterations produced, and Grant, Groff and Lewy⁸ described the clinical results obtained by the procedure. In this communication, we wish to give an account of the neurologic complications observed in a series of 19 cases after tractotomy. Although operation was performed in 24 cases, our notes on a number of early cases were regrettably brief, and in a few instances no notes were recorded. Our failure at the beginning to sharpen our observations on the neurologic complications following tractotomy was due to several circumstances. First, although certain disturbances were obvious, little concern was given them and no description made in the records, partly because it was assumed that they would be transitory and partly because our interest was captured by the sensory alterations in the face. Vigorous attempts at neurologic examination were discouraged by the presence of large cerebellar dressings, which hindered cooperation and made the subjects poor witnesses. Again, in some instances, by the time the patient was out of bed the worst of the neurologic disturbances had disappeared and the opportunity to study them had passed.

It was not long, however, before it became evident that the neurologic complications were neither negligible nor always transitory. The conclusion seemed inescapable that if the operation was to compete with other, well tested procedures, the technic would have to be so modified as to eliminate the neurologic sequels. In a previous article⁹ we outlined certain anatomic objections to the original operative description of Sjöqvist and, in turn, recommended a modification in the placing of the incision which we believe renders the operation less likely to cause neurologic complications. In brief, this modification consists in placing the incision about 12 mm. more caudally in the medulla, so that injury to the restiform body and the main and/or the lateral cuneate nucleus is avoided (fig. 1). It is admitted that in some of our earlier cases, in which the procedure described by Sjöqvist was followed, the medullary incision was inaccurately placed. Such inaccuracies, however, are inherent in a technic in which the incision must be placed so close to important structures that an error of only 1 or 2 mm. results in injury to them.

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Because of the modification in operative technic, our series of cases falls into two periods: cases in which operation was performed before, and those in which it was performed after, the adoption of the surgical modification. Of the 24 cases in which operation was carried out, the notes in only 19 are sufficiently detailed for report, for reasons already mentioned.

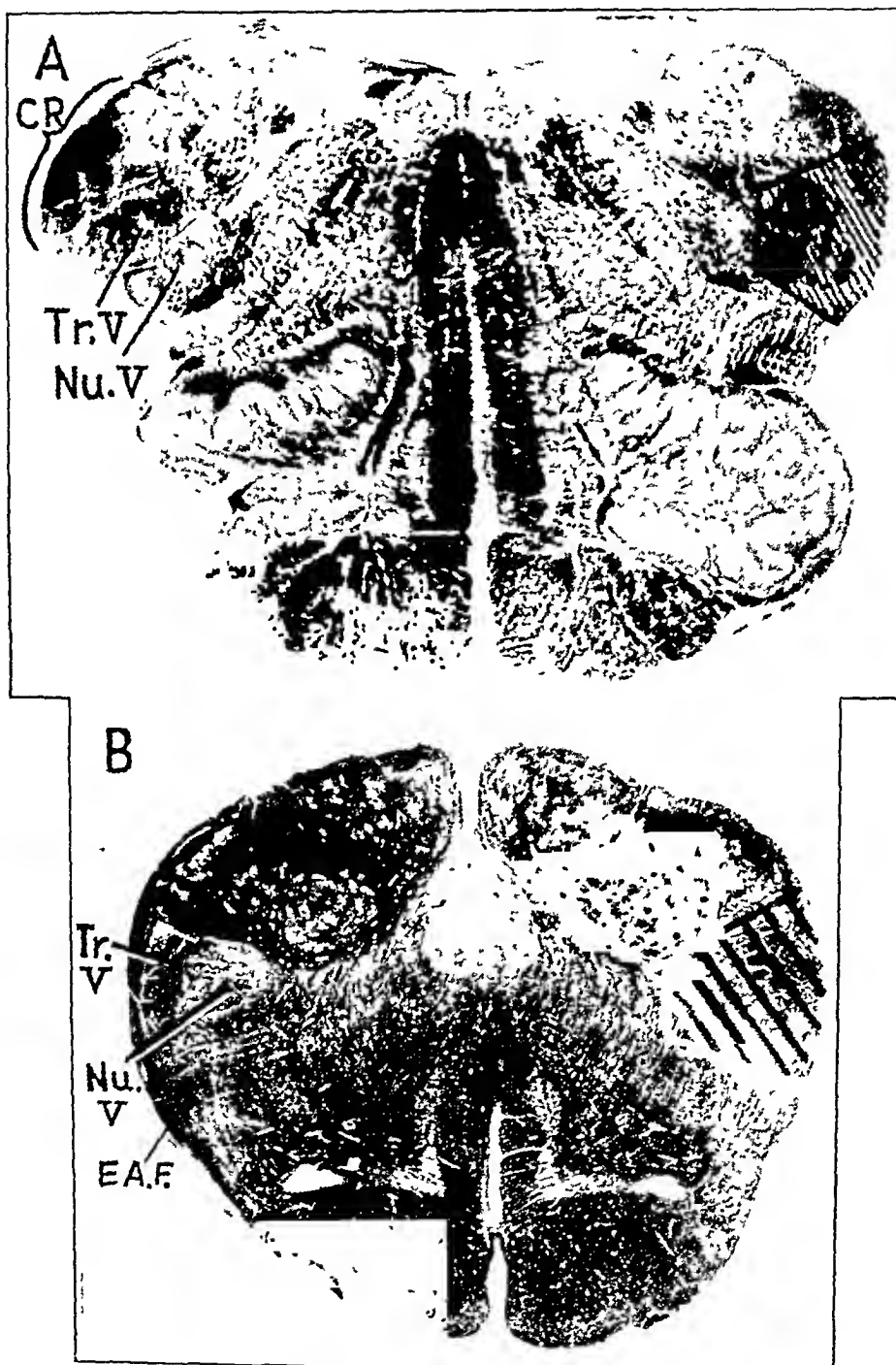


Fig. 1.—*A*, Transverse section of the medulla at the level of the middle of the inferior olive, showing degeneration of the spinal tract of the fifth nerve; Marchi stain (after Sjöqvist² [fig. 32]). The proposed incision, indicated by the shaded area, involves almost the lower half of the corpus restiforme (C. R.).

B, cross section through the medulla 4 to 5 mm. below the obex and about 2 mm. caudal to the olive. The extent of the modified incision is shown by the shaded area. At this level the descending tract of the fifth nerve (*Tr. V*) is most superficial and is covered only by a thin band of external arcuate fibers (*E. A. F.*). The spinal nucleus of the fifth nerve (*Nu. V*) is also shown to be fairly superficial.

Since autopsy studies are lacking in all but 1 of the cases to be reported, no precise correlation can be offered between the clinical disturbances observed and the nerve structures injured. However, reflection on the region of the medulla concerned permits some general speculation with regard to the structures that may have been involved. Further we cannot go; for this reason, our presentation of the cases will be purely reportorial. Inasmuch as intramedullary tractotomy is a new and still experimental operation, it seems worth while to recount as fully as possible our experiences with it, just as they occurred, and to leave for the moment the question of anatomicoclinical correlations until more autopsy material is available. The cases will be presented in the chronologic order of operation.

TRACTOTOMIES PERFORMED WITH THE ROSTRALLY PLACED INCISION OF SJÖQVIST

CASE 1.—J. E., a man aged 74, had major trigeminal neuralgia affecting the second and third divisions of the right fifth nerve. Intramedullary tractotomy was performed in April 1939.

There was conspicuous incoordination of the right arm immediately after operation. On the tenth postoperative day, when the patient was taken out of bed, he was unable to walk because of pronounced staggering and falling to the right. At this time there was still moderate incoordination of the right arm.

For several weeks after operation, and after his discharge from the hospital, the patient stated that his gait was staggering. It slowly improved over the course of several months. He also noticed that his handwriting was jerky and irregular for several months after operation.

He was seen in the follow-up clinic in January 1940, nine months after operation. He reported that he was able to walk about the house without difficulty, but that when he ventured on the street, he required the use of a cane because of mild unsteadiness of gait. Examination disclosed that he walked with a widened base and that there was a moderate degree of ataxia. He used his right leg awkwardly and was unable to walk a straight line, always stepping to the right. He staggered on attempting a quick turn. The upper portion of his body was inclined to the right in a way reminiscent of a man leaning into a wind. His right leg showed only slight ataxia in the heel to knee test, much less severe than one would expect from his disturbance in gait. There was no trace of incoordination in his right arm. His handwriting was excellent. There was no disturbance of sensation in his extremities. Power was intact in all extremities, and all the deep reflexes were normal.

He was again seen in July, fourteen months after operation. He reported that he was walking much better and had discarded his cane. He was conscious of tending to veer toward the right on walking and was aware that he tended to "throw" his right leg. It was sometimes necessary for him to "catch himself" when arising quickly from a chair or making a quick turn. On examination, it was noted that his trunk was still slightly inclined to the right. When he attempted to walk a straight line, he occasionally lurched to the right. He was able to ascend stairs rapidly and to descend them with ease. Except for these minor difficulties, his neurologic status was normal.

All three divisions of the trigeminal distribution were analgetic, and his neuralgia was completely relieved.

While the worst of the neurologic disturbances lasted only a few weeks, the patient was considerably inconvenienced for several months. We are inclined to believe that the restiform body was injured by the medullary incision.

CASE 2.—H. W., a woman aged 65, had intractable pain due to a carcinoma of the left maxillary sinus. Intramedullary tractotomy was performed in April 1939.

Unfortunately, this patient was not examined during her immediate postoperative course. However, it was noted that when she was taken out of bed, on the eighth postoperative day, there was great unsteadiness of gait and she staggered to the left. She subsequently stated that all disturbances in walking passed away two or three weeks after operation.

She was seen in June, two months after operation, at which time she had no complaints referable to the nervous system. Except for slight swaying when she was in the Romberg position and a fine nystagmus when she looked to the left, her neurologic condition was entirely normal. She was completely free of pain, and all three divisions of the territory of the left trigeminal nerve were analgetic.

The patient was one of the few who apparently escaped any serious injury of the neighboring structures, even though the medullary incision was made high in the medulla. Had our experience been limited to 1 or 2 such cases, we should also have received the impression that the procedure had few potential hazards.

CASE 3.—W. S., a man aged 53, had a questionably malignant tumor of the left maxillary sinus, which caused severe pain. Left intramedullary tractotomy was performed in April 1939.

The only note on the hospital record stated that after operation there were a moderate degree of incoordination of the left arm and moderate disturbance of gait, the patient staggering to the left. When he was seen a year later, he gave the following information: He had been "wobbly" on his feet for about a month after discharge. The clumsiness of his left hand had also disappeared in a few weeks. For several weeks after discharge he experienced numbness and tingling in the left hand and fingers. He had considerable weakness of his left hand and arm for five or six months after operation. He returned to work seven months after operation, when he was well except for slight weakness of his left arm.

He was seen in the follow-up clinic twelve months after operation, at which time he had no neurologic complaints. His neurologic condition was normal. He was entirely free of pain, the tumor having been eradicated. Sensory examination of the face showed only slight hypalgesia in the first division of the trigeminal nerve, although immediately after operation there had been analgesia in the first division and pronounced hypalgesia in the lower two divisions of distribution in the face.

This patient had sufficient neurologic disability so that he was not able to return to work for six months because of weakness of his arm. It is our impression that the alleged weakness was due to interference with postural sensation rather than to injury of the motor pathways. This inference is based on his complaint of numbness and tingling in the left hand—evidence of injury to the cuneate nucleus. This phenomenon will be more clearly illustrated in subsequent case reports.

CASE 4.—A. P., a woman aged 51, had a malignant tumor of the parotid gland. Left intramedullary tractotomy was performed in April 1939.

Immediately after operation members of the staff noted marked incoordination of the left arm. The performance of rapid alternate movements in the arm was noticeably impaired. This disturbance improved gradually after the patient's discharge from the hospital and eventually disappeared, although it is not known how long this required. A letter received from the patient about six months after operation, and written by herself, showed an even, regular script.

After operation there were analgesia in all three divisions of the trigeminal nerve and complete relief of pain.

Our information is fragmentary, but it appears that the patient suffered little inconvenience from the operation. Unfortunately, she was not carefully examined after operation.

CASE 5.—M. T., a woman aged 63, had major trigeminal neuralgia involving the third division of the left nerve. Intramedullary tractotomy was performed in May 1939.

Immediately after operation the left arm showed marked incoordination, which persisted during the patient's stay in bed, although it slowly diminished. There was no loss of power in the left extremities and no disturbance of sensation in the left arm. When the patient was placed on her feet, on the seventh postoperative day, she was unable to walk unsupported because of ataxia and falling to the left. Her gait, however, rapidly improved, and she was able to walk unsupported at the end of the second postoperative week, although her gait was slow and guarded. At the time of discharge, on the nineteenth postoperative day, there was no longer any incoordination in her arm. The disturbances in gait, as we were subsequently informed, largely disappeared within two or three weeks after operation.

The patient was seen in December, six months after operation. At that time the only difficulty she noticed was a tendency to lurch to the left when she arose quickly from a chair or made a sudden turn. The results of neurologic examination were entirely normal except that the tendency to lurch on quick movement was confirmed.

She was again seen in the follow-up clinic in July 1940, thirteen months after operation. There was no neurologic complaint of any kind, nor did examination disclose any neurologic disturbances. The left side of her face, which had been completely analgetic after operation, had now regained sensation completely. There was no return of the neuralgia, although she occasionally experienced slight quivering and burning sensations at the angle of the mouth.

Although the incision in this case was also made high in the medulla, the subsequent neurologic complications were mild and lasted but a few weeks. Their brief duration may have been due, however, to the fact that the incision was not made deep enough to produce lasting analgesia. Had this been done, it is possible that the neurologic complications would have been more severe. Our reason for saying this will be stated later.

CASE 6.—R. A., a man aged 49, had symptomatic trigeminal neuralgia involving the second division of the left nerve, apparently due to multiple sclerosis. Neurologic examination before operation showed moderate ataxia of gait and moderate incoordination of both upper extremities, tremor of the head, nystagmus, slight spasticity of the legs, hyperreflexia and a Babinski sign on the left side. Left intramedullary tractotomy was performed in June 1939.

After operation there was a decided increase in the ataxia of the extremities on the left side. The patient was able to walk with a little support. No other notes were made during the immediate postoperative period. There were analgesia of the lower two divisions of distribution of the trigeminal nerve in the face and relief from neuralgic pain.

The patient was seen in September, two and one-half months after operation. He stated that since operation his gait had been so unsteady that people thought him drunk. Examination showed severe difficulty in gait, with staggering to the left, but he could walk unsupported. Although there was considerable ataxia of all four extremities, the left arm and the left leg were more affected than the right. Difficulty in performing rapid alternate movements was especially noticeable in the left arm. Sensation was intact in all extremities.

The patient was seen again in May 1940, eleven months after operation. He still complained of difficulty in gait and required support to walk. Although he was ataxic in all extremities, the left arm and leg were more affected than the right. The sensory defect produced in his face by operation had largely disappeared, and he again experienced attacks of trigeminal neuralgia. He was readmitted to the hospital, and a retrogasserian neurectomy was performed.

It is difficult to pass judgment on the neurologic effects of tractotomy in this case because of the associated diffuse disease of the central nervous system. It may be, of course, that the increase in symptoms represented merely the usual progression of the disease. On the other hand, the patient was more incoordinate after the operation than before; so we feel that the operation must be held responsible for part, if not for all, of the increase in symptoms and signs. It must not be overlooked, however, that neurologic compensation is less likely to occur in an already severely damaged nervous system, and this may explain the patient's protracted difficulties from our incision, even though it was not deep enough adequately to relieve pain.

CASE 7.—F. W., a man aged 65, had a painful carcinoma of the right cheek. Right intramedullary tractotomy was performed in August 1939.

On the second postoperative day a confusional psychosis developed, and the patient was entirely inaccessible to examination. He was taken out of bed on the tenth postoperative day and placed on his feet. He could not stand or walk without support and constantly fell to the right. The pronounced incoordination of gait was still present on the thirteenth day, when it became necessary to remove him to an institution. He remained psychotic until his death, two months later, and we were unable to obtain any further information concerning his neurologic status.

Although we were not able to examine this patient, it was our impression that there was considerable neurologic disability, most evident in disturbances of gait and equilibrium.

CASE 8.—E. V. B., a man aged 56, had major trigeminal neuralgia affecting the second division of the right nerve. Right intramedullary tractotomy was performed in August 1939.

Immediately after operation incoordination was marked in the right arm and present, although mild, in the right leg. When he was placed on his feet, on the eleventh postoperative day, there were considerable staggering and falling to the right. At the time of discharge from the hospital, on the sixteenth postoperative day, he still required support in walking because of staggering. He subsequently told us that there was a decided stagger in his gait for several weeks after discharge and that because of it he was not able to walk straight. His family noted that he tended to incline his trunk to the right side and that he veered to the right when

walking. His right arm also remained awkward and clumsy for several weeks after his return home. He had not noted any unusual sensations in his hand.

The patient was seen in the follow-up clinic in January 1940, five months after operation. He admitted that there was still slight disturbance in gait, which was not noticeable under ordinary circumstances. He had gone back to work as a carpenter but noticed that he frequently missed nails that he was hammering and that his arm felt a little clumsy when he was using tools. The latter complaint was largely subjective, since his work did not suffer because of it.

Examination showed little neurologic disturbance. He walked with a slightly widened base and lurched occasionally to the right when making a sudden turn on command or when walking fast. With his eyes open, he walked in a perfectly straight line but tended to veer to the right with his eyes shut. In spite of the alleged clumsiness of his right arm, clinical tests failed to show any evidence of incoordination. The rest of the neurologic examination also gave normal results.

The patient was seen again in the follow-up clinic in July, eleven months after operation. He still noticed that when he walked too fast or too far his gait became a little unsteady and he tended to veer to the right. His ability to use hammer and nails had improved, and he stated that he only occasionally missed. On examination he made an occasional sideward step to catch himself when he was walking with his eyes closed. Other than this minor defect, the results of neurologic examination were normal. Sensory examination of the face showed analgesia in all three divisions of the fifth nerve, and there was complete relief of pain.

The neurologic complications observed in this case were probably due to associated injury of the restiform body. The patient was largely incapacitated for two or three weeks after operation but made an essentially complete recovery within four to six weeks after operation.

CASE 9.—R. J., a man aged 45, had carcinoma of the tongue and severe, intractable pain. Left intramedullary tractotomy was performed in December 1939. In addition, the glossopharyngeal nerve and the posterior roots of the upper three cervical nerves were sectioned.

Examination on the second postoperative day revealed pronounced incoordination of the left arm when the eyes were closed and a somewhat less severe disturbance with the eyes open. Investigation showed that, in addition to the cerebellar component, there was a considerable degree of ataxia in the left arm referable to the posterior column. Postural sensation was almost absent in the fingers and was decreased as high as the elbow. There were pseudoathetotic movements of the fingers of the left hand. Power was decreased almost 50 per cent in the left arm and the left hand grip as compared with that in the right. The deep reflexes in the left arm were slightly decreased as compared with those in the right arm. Power was intact in the lower extremities. There was slight ataxia in the left leg in the heel to knee test. The patient complained of numbness and tingling in the fingers of the left hand. In spite of the impairment in postural sensation, vibratory perception in the fingers of the left hand was equal to that in the fingers of the right hand. There was no loss of cutaneous sensation.

During the subsequent postoperative days the incoordination of the left arm lessened and power slowly returned. Nine days after operation, however, there was still considerable impairment of postural sensation in the hand and fingers on the left side. The hand was numb and tingling. At this point examination revealed no disturbances in stereognosis, although objects were handled clumsily. When the patient was placed on his feet, he was unable to stand or take steps unsupported, but staggered and fell to the left side. He seemed utterly unable to maintain his body balance. Although there was still incoordination of the left arm, little or none was elicitable in the left leg by ordinary tests; it seemed, therefore, that the disturbances in equilibrium could hardly be accounted for on the basis of involvement of the cerebellar pathways. The phenomenon appeared to be vestibular.

When he was discharged, on the fourteenth postoperative day, he was still unable to walk without assistance, although the ataxia was less severe. The disturbances in the left arm were still present, but were greatly improved over his immediate postoperative status.

The patient lived two and one-half months after operation. A letter received from his wife just before his death stated that he was able to walk but staggered to the left, that his left arm and hand were clumsy and that he still experienced numbness in the left hand.

After operation there were analgesia in all three divisions of the trigeminal nerve and analgesia and anesthesia of the pharynx and the left side of the neck. The patient was free

of pain until shortly before he died, at which time pain developed in the top of his head, doubtlessly as a result of metastases.

From the nature of the neurologic disturbances, it is likely that the cuneate nuclei, as well as the restiform body, were injured by the medullary incision although the production of analgesia of the face indicates that the incision was placed with some degree of accuracy. The peculiar disequilibrium, which appeared to be vestibular in nature, raised the suspicion that the vestibulospinal tract was injured. This case illustrates the potential hazards of an incision placed in such close proximity to important nuclei and tracts. Had the patient lived longer, there would doubtless have been considerable improvement in his neurologic status; he was, nevertheless, seriously handicapped for two and one-half months.

CASE 10.—C. K., a man aged 55, had a carcinoma of the tongue which was infiltrating the mandible and causing severe, intractable pain. Right intramedullary tractotomy was performed in January 1940.

Twenty-four hours after operation examination disclosed wild incoordination of the right hand, the arm being useless for almost any task. The patient complained of feelings of numbness and tingling in his right hand and fingers. There were conspicuous pseudoathetoid movements of the outstretched hand and fingers. Postural sensation was almost absent in the fingers and considerably impaired at the right wrist. There was definite dysstereognosis in the right hand, the patient being unable to identify simple objects, although he could recognize some of their attributes, such as roundness or angularity. He could not differentiate cloth from paper or roughness from smoothness. In addition, he could not properly estimate the weight of objects placed in his right hand. He consistently stated that the object in his right hand was lighter than that in the left, when in reality it was considerably heavier. Vibratory sensation, as tested with the clinical tuning fork (128 double vibrations per second), was as well perceived in the hand and fingers on the right side as in those on the left. There was mild weakness of the right arm and the right hand grip. The right leg showed only slight incoordination in the heel to knee test. Cutaneous sensation was intact in both right extremities. Nystagmus was not present.

On the third postoperative day the status was much the same except that the signs had all diminished in intensity. The weakness of the grip in the right hand seemed more evident, however. Sensory examination of the face disclosed only slight hypalgesia in the lower two divisions of the fifth nerve.

On the seventh postoperative day there was still pronounced incoordination of the right arm, which seemed to be about equally compounded of cerebellar dyssynergia and posterior column ataxia. Power was still noticeably reduced in the right hand and the right arm. The deep tendon reflexes in the right arm were less active than those in the left. Postural sensation was still greatly impaired in the fingers of the right hand. Vibratory sensation was intact. There was still dysstereognosis in the right hand. The incoordination of the right leg had almost disappeared. His neurologic condition slowly improved, although his general condition was poor. He was discharged on the sixteenth postoperative day.

The patient was examined in his home twenty-four days after operation, and two weeks before his sudden death from laryngeal edema. At the time of examination he was found sitting in an easy chair. He had not been able to feed himself because of the incoordination in his arm. He was able to stand unsupported with his legs spread wide apart but promptly fell to the right on his attempting the Romberg maneuver. When he fell, he made no movements of postural adjustment to "catch himself," but fell en masse, like a statue. When he was supported and encouraged to take steps, his trunk inclined far to the right. The tilting of the body, the tendency to fall and the pronounced staggering reminded one of a severe vestibular disturbance. The extreme disturbance of equilibrium and the trunkal ataxia were entirely out of proportion to the slight evidence of incoordination in the right leg when the patient was tested lying down. On attempting to walk, however, he handled his right leg awkwardly. There were decided "drifting" of his right arm when it was held outstretched and constant pseudoathetoid movements of the fingers, of which he was not aware. The incoordination of the right arm was still pronounced, but considerably less so than when he was discharged from the hospital. The impairment of postural sensation in the fingers and hand on the right side was about the same as at the time of discharge, being almost complete in the fingers. The dysstereognosis was still present, the patient being able to do no more than recognize certain qualities of objects placed in his hand. Vibratory perception and cutaneous sensations were intact in the right hand. Two point discrimination

was slightly impaired. He was still unable to judge the relative weights of objects with his right hand. There was no alteration of tone in the right arm, but the weakness of the hand grip was still easily evident.

It was the examiner's opinion that there had been moderate improvement in the incoordination of the right arm but that the impairment of postural sensation in the right hand and the disturbance of gait had shown little or no improvement since the patient's discharge from the hospital. There was slight hypalgesia in the lower two trigeminal divisions of the face. This had been sufficient to ameliorate his pain, but not to relieve it entirely.

In this case, and in case 9, the evidences of neurologic injury were most severe. One wonders how long it would have taken for complete recovery to have occurred. Apparently, neurologic compensation takes place more quickly when the injury is confined to the restiform body than when both it and the cuneate nuclei, and possibly the vestibulospinal pathways, are injured. Moreover, the disturbances in postural sensation and in equilibrium appear to persist longer than does the cerebellar dyssynergia.

It was realized at the operating table that the incision had been extended too far dorsally and that the restiform body and the cuneate tubercle had been partly cut across. It was thought at the time, although proved wrong later, that the incision had been deep enough to sever the descending tract of the trigeminal nerve. Although permission for autopsy was not granted, and therefore the exact extent of the lesion could not be verified, it is believed that the neurologic signs witnessed represented the combined syndrome of the restiform body and the cuneate tubercle. The vestibulospinal tract was possibly also injured. The interesting and important physiologic information derivable from instances of this kind will be discussed in a subsequent communication.

TRACTOTOMIES PERFORMED WITH THE MODIFIED INCISION

The opportunity to perform autopsy in a case in January 1940 in which operation had been done in May 1939 furnished us with a clue that led to modification of the technic. When the brain stem was sectioned, it was observed that the medullary incision had been made 8 mm. below the level of the obex, whereas we had previously been accustomed to make it several millimeters above the level of the obex (fig. 2). This fact had not been recognized at the operating table.

However, as the subsequent history (case 11) shows, the patient had complete analgesia in all three divisions of his face. This observation suggested that, contrary to general opinion, all divisions of the trigeminal nerve are represented in the descending tract at a low level in the medulla. It had been thought that the fibers from the mandibular and maxillary divisions terminated in the spinal nucleus of the trigeminal nerve at a rather high level in the medulla, which may have accounted for Sjöqvist's placing the incision in the descending tract at a point opposite the open fourth ventricle. With this new information, it was apparent that the incision could be made routinely at a more caudal level of the medulla, with, at the same time, much less chance of injuring the restiform body. Because the lower portion of the medulla could be visualized more clearly, there was also less likelihood of injury to the posterior column or the cuneate tubercle. The subsequent 8 cases, cases 12 to 19, illustrate the results of the modification.

CASE 11.—H. H., a man aged 55, had carcinoma of the right mandible. Right intramedullary tractotomy combined with section of the glossopharyngeal nerve and the posterior roots of the upper three cervical nerves was performed in May 1939. There was no information on the immediate postoperative course, but the note at the time of discharge stated briefly that there were pronounced staggering and falling to the right but no incoordination of the right arm.

The patient was examined at another hospital in January 1940, eight months after operation and three weeks before his death. He had undergone resection of the mandible several

weeks previously, as a result of which he could not speak; the neurologic history in the interval could not, therefore, be obtained. The patient was able to stand and walk unsupported, although his base was widened and he occasionally lurched to the right. The upper part of his trunk was slightly inclined to the right. He fell to the right on performing the Romberg maneuver. There was no evidence of weakness or of incoordination in his right arm. There was slight ataxia in the right leg in the heel to knee test. All the reflexes were equal on the two sides.

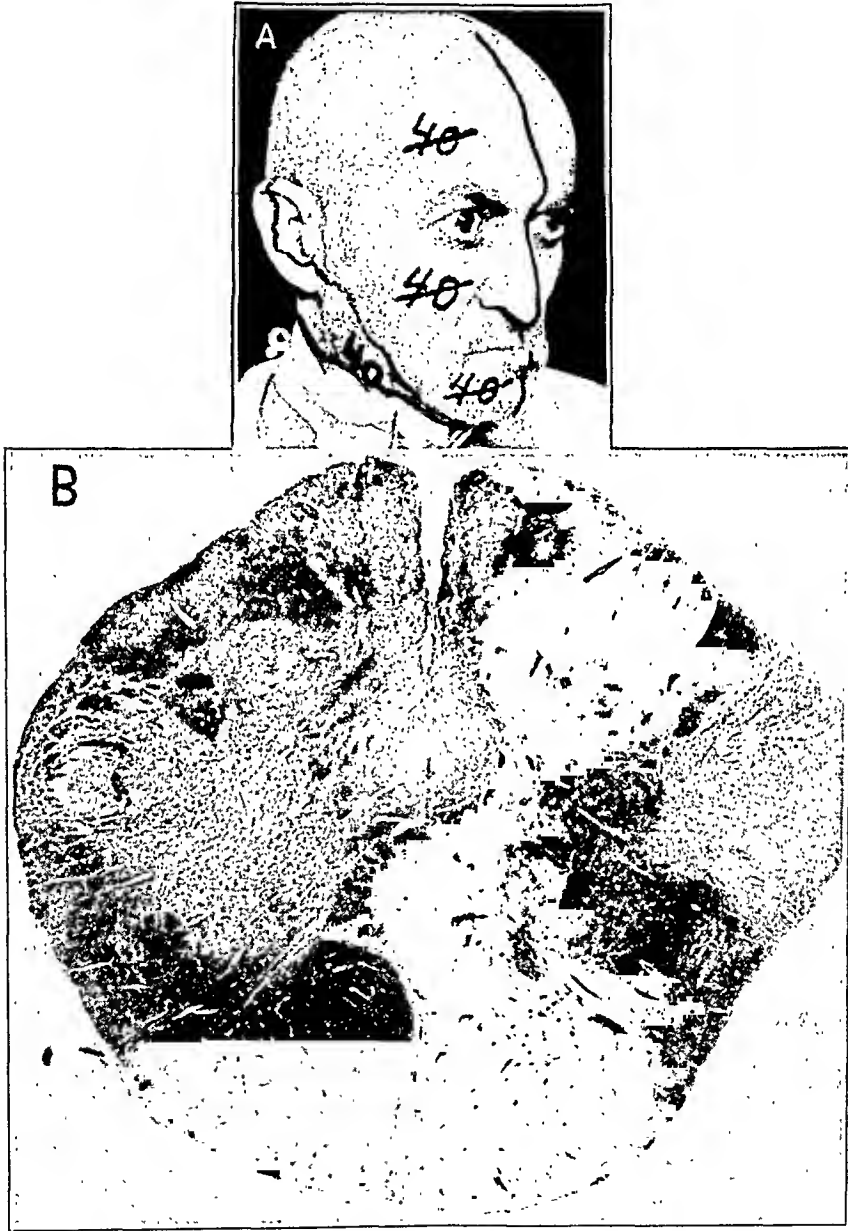


Fig. 2. (case 11).—*A*, postoperative photograph of the patient, showing areas of sensory loss. The numeral 40 with the line drawn through it means that more than 40 Gm. of pressure with a Head algometer failed to provoke pain sensation—in other words, analgesia.

B, section through the medulla 7 to 8 mm. below the obex. The demyelinated, wedge-shaped area of destruction represents the site of the surgical incision (tractotomy), which encompasses the descending tract and the spinal nucleus of the trigeminal nerve. Judging from the complete analgesia of the right half of the face, all three divisions of the trigeminal nerve are represented in the descending tract at this level of the medulla.

Sensory tests disclosed hypalgesia of the left side of the body and extremities, with preservation of touch sensation. The right side of his face was analgetic, and the pharynx

and the right side of his neck were anesthetic and analgetic. The analgesia of his face and neck was so profound that the resection of the mandible had been accomplished without the use of an anesthetic agent.

The patient's extreme cachexia and weakness enhanced the neurologic signs, which, however, were not extreme. As a matter of fact, it is difficult to account for their presence, since sections of the brain stem secured at autopsy (fig. 2) showed that neither the restiform body nor the cuneate nucleus had been injured. This was the only case in our series in which a crossed sensory syndrome (Wallenberg syndrome) occurred as a complication. Possibly the result indicates that the incision was placed a trifle too deep and ventral.

Schwartz and O'Leary¹⁰ recently reported on an experimental operation in which they transected the lateral spinothalamic tract in the medulla oblongata for the relief of pain in the upper portion of the arm and the upper part of the chest, areas which are difficult to render analgetic by the classic chordotomy. They succeeded in producing hypalgesia of these regions by incising the medulla to a depth of 6 mm. at a point just dorsal to the caudal end of the inferior olive. The concept of section of the spinothalamic tract in the medulla for the relief of pain about the shoulder and neck had occurred to us in 1939, as a result of our experiences with tractotomy, but a suitable case did not present itself. However, the feasibility of the procedure is confirmed by our experience in a case in which the lateral spinothalamic tract was inadvertently severed at operation, in 1939.

As has been mentioned, the significant observation derived from this case is that analgesia of the face may be produced by an incision more caudal than had heretofore been made. In the next case to be described the incision was deliberately placed more caudally than in the earlier cases, although not as far as that in case 11.

CASE 12.—J. S., a minister aged 58, had severe major trigeminal neuralgia involving the first and second divisions of the left nerve. Left intramedullary tractotomy was performed in March 1940.

The patient was carefully examined eight hours after operation. There was wild incoordination of the left arm, so severe that he struck himself in the face on attempting to touch his nose. He complained of numbness and tingling in the left hand and fingers. Postural sensation was absent in the fingers of the left hand and was greatly impaired at the wrist. Vibratory perception was intact, however. Stereognosis was not disturbed in the left hand. Power seemed to be equal in the two upper extremities. There was moderate incoordination of the left leg.

The patient was again examined forty-eight hours after operation. There was rotatory nystagmus on his looking to the right. The incoordination of the left arm was pronounced, but was less severe than immediately after operation. The incoordination was due as much to loss of postural sensation in the hand as to the cerebellar components. He still complained of numbness and tingling in the left hand.

On the fifth postoperative day the incoordination of the left arm was much decreased. He was able to recognize the position of his fingers in space when the stimulus was strong. Power was equal in his upper extremities. There were no disturbances in cutaneous sensation. The left leg showed mild ataxia in the heel to knee test. The nystagmus had disappeared.

The patient was taken out of bed on the sixth postoperative day. He was entirely unable either to stand or to walk because of severe disturbance of equilibrium. He spread his legs far apart in an effort to stand but promptly fell over to the left. There were no reactions of defense in order to balance himself, and he fell over like a toppling statue.

On the seventh postoperative day the patient was able to stand unsupported with his legs straddled, but fell over on attempting to take a step. The upper part of his body tilted far over to the left. The inclination of the trunk, the severe disturbance of equilibrium and the inability to make defensive balancing motions, along with the immediate falling to the left

10. Schwartz, H. G., and O'Leary, J. L.: Section of the Spino-Thalamic Tract in the Medulla with Observations on the Pathways for Pain, *Surgery* 9:183, 1941.

when he attempted to walk, seemed to represent a severe vestibular disturbance. The left leg was handled clumsily but showed only slight incoordination in the heel to knee test, far less than one would expect from the disturbance of gait. The left arm showed now only a mild degree of incoordination, and the patient could use it for simple tasks. He complained of tingling in the left hand, but the sense of numbness had disappeared. The disturbance in postural sensation in the fingers had largely disappeared, although it was still present to a slight degree.

On the eighth postoperative day the patient was able to take a few steps by carefully watching his feet but fell over on looking away. His trunk was carried strongly inclined to the left. He stood with his legs wide apart and fell over on bringing them together. The incoordination of his left arm was slight, and there was only mild impairment in the performance of rapid alternate movements. A slight rebound phenomenon was elicitable in the left arm. In the left leg there was just a trace of ataxia when he performed the heel to knee test. The disturbance of postural sensation in the left hand had disappeared, although he still complained of a continuous tingling sensation. The striking observation was the marked disturbance in equilibrium and body posture, as compared with the slight evidences of incoordination when the extremities were tested separately.

On the tenth postoperative day the patient was able to walk the length of the hospital room unsupported, but he moved with short, shuffling and guarded steps. He frequently staggered and lurched to the left and completely lost his balance on making a turn. His inability to make the necessary postural adjustments to rescue himself from falling was still conspicuous. There was no longer any evidence of dysmetria or dyssynergia in the left arm, as judged by the usual tests. Past pointing was not present.

On the twelfth postoperative day he was able to walk fairly well unassisted, although he staggered to the left every six or eight steps. His gait was shuffling and guarded; when he was encouraged to take long steps, his gait became unsteady, he would cross his legs and, if not caught, would fall. He was able to stand in the Romberg position for ten or twelve seconds; then he would sway and fall over. The usual reactions of defense to threatened loss of balance were absent. He made no attempt to throw out his arms or shift his stance or center of gravity, but fell over like a statue. He stated that he did not realize he was falling until it was too late to regain balance. If his pelvis was passively tilted backward or to the left, he made no counterreflexes to regain equilibrium. Although the left arm and hand showed no neurologic abnormalities, he still complained of tingling in his fingers.

He continued to improve from day to day, and on the sixteenth postoperative day his gait and postural reactions showed only mild disturbances. He walked freely but tended to veer to the left and occasionally made a sideward step. He could not, however, walk a line or balance himself standing heel to toe. He was able to stand in the Romberg position.

The patient was discharged on the eighteenth postoperative day. At this time his gait was almost normal except that he occasionally lurched to the left. He still staggered a little on making a sudden turn. The postural reactions to his being placed off balance were still greatly impaired, although they were improved. He was able to walk up stairs easily but not down stairs, as he could not balance himself and would have plunged headlong if he had not been protected. He had a subjective feeling of insecurity in using his left hand, but the usual gross tests showed nothing abnormal.

There was analgesia of all three divisions of the trigeminal nerve on the left side of his face, with complete relief from pain.

The patient was seen in the follow-up clinic in April, just one month after operation. Except for minor difficulties, his neurologic status was normal. He walked with a slightly widened base. When he rose quickly from a chair, he lost balance and tended to stagger to the left. He walked freely and easily. He stated that his left hand was a little clumsy in handling table utensils or buttoning his clothes, but the usual tests showed nothing abnormal. There was still a deficiency in making his postural adjustments to regain equilibrium when his body was passively tilted to the left.

A letter was received from the patient in July, three months after operation. He had resumed his ministerial duties. There were several minor complaints. The tingling still persisted in his fingers but was mild. He confessed to a little awkwardness in the use of his left hand when he performed complicated movements. He had typewritten his letter, and he apologized for the many errors in it, saying that the fingers of his left hand did not hit the keys properly. When he was fatigued or when he walked too long, his gait became a little unsteady. Other than these complaints, he was vigorous and in perfect health. He was well pleased that his neuralgia had been relieved without production of numbness in his face.

Because the neurologic signs were studied more intensively in this case than in any other, one may have the impression that the postoperative neurologic complications were severe. As a matter of fact, the patient had recovered, for all practical purposes, on the thirteenth to fifteenth day after operation. However, it appears that the incision was made still too far rostrad and that the restiform body and the cuneate nuclei were injured, although not seriously so. From the experience gained in this case, it was decided to move the incision a trifle more caudally and ventrally in subsequent cases.

CASE 13.—N. E., a woman aged 47, had major trigeminal neuralgia affecting the second and third divisions of the right nerve. Right intramedullary tractotomy was performed in April 1940.

Eight hours after operation the patient was comfortable and cooperative. Slight nystagmus was present on her looking to the right. There was slight incoordination of the right arm. Power was unaffected, and the reflexes were equal on the two sides. There were no tingling sensations in the right hand, and postural and all other modalities of sensation were intact.

Twenty-four hours after operation there was just a trace of incoordination in the right arm. Alternate movements were well performed, but a slight degree of rebound phenomenon was noted in the left arm. There was no incoordination in the right leg. Stereognosis was intact. There was analgesia in all three trigeminal divisions of the face.

On the third day after operation there was no evidence of any neurologic abnormality when the patient was examined in bed. She was then placed on her feet, but she could neither stand nor walk unsupported. There was severe disturbance of equilibrium, and she was utterly unable to balance herself. On falling she made no efforts to regain her balance through the use of the usual posture reflexes. Again, the disturbances in gait and equilibrium were accompanied by complete absence of cerebellar symptoms when she was examined in bed.

On the fifth postoperative day she was able to walk a few steps unsupported, although her base was widened and she lurched to the right. She always "caught" herself, however, and did not fall. She was unable to stand in the Romberg position but fell promptly to the right.

On the seventh postoperative day her gait had so improved that she was able to walk unsupported. Her gait was slow and guarded, however, and she frequently staggered to the right. She could not walk a straight line, stand with her feet together or stand in the heel to toe position. She still was unable to make the correct postural adjustments to regain balance when her pelvis was passively tilted to the right.

Her neurologic difficulties rapidly cleared up, and she was discharged on the thirteenth postoperative day. With minor exceptions her gait and equilibrium were normal. She stated that her right leg felt a little awkward, and when she walked the right leg swung farther laterally than the left. If she was forced to walk rapidly, she tended to stagger to the right. With her eyes closed she veered to the right. She was still unable to walk in a straight line.

The patient was seen in the follow-up clinic in May 1940, one month after operation. She noted a little clumsiness of the right leg on going up or down stairs, but otherwise felt entirely well. She was taking complete care of her house. On examination, nothing abnormal could be detected until she was asked to descend stairs. Then it was noted that her right leg did not act with quite the facility of the left.

She was again examined in June, two months after operation. No neurologic signs could be observed. She was relieved of her neuralgia, and sensory examination showed analgesia in all three divisions of the trigeminal nerve.

The patient made a quick recovery and was, for all practical purposes, neurologically normal by the eighth or ninth postoperative day. This case demonstrates why a patient must be examined directly after operation if one is to observe the neurologic disturbances. If this patient had been kept in bed eight or nine days before we tested her gait, we should not have known that there was any disturbance and therefore should have thought that the complications were very mild and transient and that they were confined to the arm. By getting the patient out of bed on the third or the fourth day we were able to observe phenomena that other-

wise would have been missed. At this stage we felt that we had fairly well solved our problems concerning the placement of the incision. Further experience seemed to confirm this belief, although, as will be shown, the results were not constant.

CASE 14.—A. W., a woman aged 63, had major trigeminal neuralgia involving the third division of the left nerve. Left intramedullary tractotomy was performed in June 1940.

The patient was examined five hours after operation. There was no incoordination of the left arm. Nystagmus was not elicited. Sensation was intact in the left hand and fingers, and there were no subjective complaints. Analgesia existed in all three divisions of the trigeminal nerve.

Twenty-four hours after operation the patient was perfectly comfortable. A complete neurologic examination gave entirely normal results.

The patient was taken out of bed on the seventh postoperative day. She walked slowly and guardedly, but not more so than one would expect to see in an elderly woman who had been confined to bed for a week after a cranial operation. There were no evidences of neurologic disturbance. She was discharged on the twelfth postoperative day, with complete relief of her neuralgia and with analgesia of all three divisions of the trigeminal nerve.

This patient, who was observed intently, showed no evidence of neurologic injury after operation, a fact which we assign to the modification in technic. Although we did not examine her gait until the seventh postoperative day, its normality at that time argues against any considerable disturbance earlier in the postoperative course.

CASE 15.—R. P., a man aged 74, had carcinoma of the lower gum on the left side. Left intramedullary tractotomy was performed in June 1940.

Eight hours after operation neurologic examination showed that the left upper extremity was normal in all respects. The patient had no complaints referable to it. There seemed to be slight incoordination of the left leg, as indicated by the heel to knee test.

The patient was placed on his feet on the second day. He could stand unassisted with his legs spread apart, but fell to the left on placing his feet together or on attempting to take a step. The disturbance in equilibrium was far greater than one would expect from the results of neurologic examination with the patient in bed. The left leg was handled clumsily.

The disturbances of gait rapidly improved, and by the seventh postoperative day the patient was able to walk around the ward. His gait was guarded, and the steps were short, but this was due to his age and general weakness rather than to injury of the nervous system. On the ninth postoperative day an abscess of the left calf developed as a result of thrombophlebitis. He was not able to be out of bed again until the twenty-fifth postoperative day. At this time his gait showed no disturbance due to any neurologic disability, but because of his weakness, long hospitalization and loss of weight, it was shuffling and slow. He was discharged on the twenty-ninth postoperative day. The pain in his face was not completely relieved but was greatly improved. There was only slight hypalgesia in all three divisions of the trigeminal nerve.

We felt that by the seventh postoperative day the patient had recovered from whatever neurologic insult was present. Had he remained in bed for a week before complete neurologic examination, we should have thought that there was no neurologic impairment, since nothing was observable in the arm. The incision, obviously, was not made deep enough, since sensory tests of the face indicated that the descending tract had not been entirely transected. Although this error made the result somewhat unsatisfactory, the absence of severe or persistent neurologic signs again suggested that the major complications of the operation could be avoided by placing the incision in the descending tract 4 to 6 mm. below the obex.

CASE 16.—G. S., a man aged 49, had bilateral major trigeminal neuralgia affecting the second and third divisions on the right side and the second division on the left side. Left intramedullary tractotomy was performed in September 1940. At the same time, the sensory root of the right trigeminal nerve was sectioned in the posterior fossa.

Immediately after operation there was considerable incoordination of the left arm. The patient also complained of numbness and tingling in the left hand. There was no gross

disturbance either in postural sensation or in stereognosis. The left leg was clumsy when the patient was taken out of bed on the seventh postoperative day, and there was considerable staggering to the left. Improvement was rapid, and on his discharge the staggering was much less severe.

The patient later stated that he continued to lurch to the left side for about three months and that his left hand was awkward for about two months after operation. He was seen in the follow-up clinic in February 1941, five months after operation. He still complained of some unsteadiness of gait and the tendency to lose his balance and fall to the left. While shoveling coal, he had lost his balance and fallen, slightly injuring his knee. In addition, he stated that there was a sensation of numbness in his left forearm, which "ran down" into his thumb. His thumb constantly prickled. Examination showed slight incoordination in movements of the left arm.

He was again seen in the follow-up clinic in June, nine months after tractotomy. He stated that the tingling sensation still persisted in his left thumb, although it was much less marked. He also noticed that he frequently dropped table utensils from his left hand without realizing it until after they fell. When he did not "watch himself," he tended to stagger to the left. On examination it was noted that he used his left leg a little awkwardly and that with his eyes shut he veered and occasionally lurched to the left, although he always recovered himself. He was able to walk heel to toe with his eyes open. On descending stairs, he kept close to the wall, as he was unsteady. Except for these minor disturbances, his gait gave him no trouble. There was no evidence of incoordination in the usual tests. With his eyes closed, however, he could not place his finger accurately on the point of his nose. This appeared to represent a slight difficulty in postural sensation, but ordinary tests could not disclose any gross disturbance. He could identify all objects, as well as textures, with his left hand, but greater subjective effort and more time were required than with the right hand. Vibratory perception was intact, as were all modalities of cutaneous sensation. The left leg was slightly, but definitely, clumsy in the heel to knee test.

The right side of his face was entirely anesthetic as a result of section of the root. The left (tractotomized) side of his face was hypalgetic in the first division and moderately hypalgetic in the third division of the trigeminal nerve. In the second division there was only a slight degree of sensory loss, and this was patchy. The patient complained of attacks of "soreness" in the second division, associated with twitching sensations, which probably represented a beginning return of the trigeminal neuralgia.

In spite of precautions to place the incision at least 5 mm. below the level of the obex, there was undoubtedly some injury of the corpus restiforme and the cuneate nuclei. However, the neurologic disturbances, although fairly pronounced and persisting for several months, were not nearly as severe as those noted in some of the earlier cases. This case, again, illustrates how it is possible to injure important structures without securing adequate analgesia in the necessary trigeminal division, an example of the capricious results that are not always avoidable with tractotomy, even though great care is taken in placing the medullary incision.

CASE 17.—B. Alt., a woman aged 53, had major trigeminal neuralgia involving all three divisions of the right nerve. Right intramedullary tractotomy was performed in October 1940.

The patient, unfortunately, was not examined during her early postoperative course. On the tenth day in the hospital a moderate degree of incoordination was noted in the right arm. Her gait was unsteady, and she veered to the right. She could ascend stairs without difficulty but was unable to descend them without help, as she lost her balance and fell forward. She was unable to walk in a straight line but lurched to the right.

Later, in a follow-up interview in February 1941, four months after operation, she remarked that she had been a little "wobbly" on her feet for three or four weeks after discharge, but this had cleared up entirely. During her stay in the hospital her right hand felt numb and tingled, and this had persisted, although it became less intense. She said that her right hand still felt "stupid," by which she meant that it was still a little clumsy and weak. Neurologic examination gave entirely normal results.

She was again seen in the follow-up clinic in June, eight months after operation. She still complained of a slight numbness and tingling sensation in the right thumb. She occasionally dropped articles from her right hand without being aware of it. The neurologic examination revealed nothing abnormal. There was not the slightest residual disturbance of gait.

Her trigeminal neuralgia was completely relieved, and the entire right half of her face was analgetic. She complained, however, of slight burning and aching about her right eye. This mild dyesthesia had occasionally been noted in other cases after tractotomy.⁷ She was completely satisfied with the result of operation.

The mild and short-lived neurologic disturbances following tractotomy in this case were unquestionably due to the fact that the incision had been precisely placed in the descending tract, without any noteworthy injury of contiguous structures. However, as previous experience had shown, if this patient had been thoroughly examined immediately after operation, a much more severe disability might have been observed. .

CASE 18.—J. Sch., a man aged 41, had major trigeminal neuralgia of the second and third divisions of the right nerve. Right intramedullary tractotomy was performed in December 1940.

On first examination, five days after operation, the patient was able to stand unsupported but staggered to the right on attempting to walk. He complained of numbness of the right hand and fingers. There was a mild degree of incoordination of the right arm. On the seventh postoperative day he was ambulatory and required no help in order to get about the ward. He still tended to stagger to the right but recovered himself.

He was seen in the follow-up clinic in May 1941, approximately five months after operation. He still staggered a little to the right when he walked, but this was readily compensated for. He complained that his right hand and forearm felt numb and tingled.

He was again seen in the follow-up clinic in June 1941, six months after operation. He stated that for about four months after operation he was annoyed by his tendency to lurch to the right when he walked, but this disturbance had practically disappeared. He still noticed that his right hand tingled slightly, but he had no difficulty in handling objects. A thorough neurologic examination revealed no abnormalities except that in walking with his eyes closed he occasionally lurched to the right, but instantly recovered himself.

Sensory examination of the face disclosed that the first and second divisions were entirely analgetic and the third division was notably hypalgetic. In spite of the analgesia in the second division, the patient complained of typical, although not severe, paroxysms of trigeminal neuralgia. There was, in addition, a definite "trigger point" on his upper lip, contact with which precipitated a paroxysm.

Although the neurologic disturbances persisted for several months, they were mild and hardly interfered with the patient's activities. As far as the neurologic aspects were concerned, the outcome in this case was satisfactory. However, the presence of a trigger point and neuralgia in an analgetic area is unique in our experience and raises the speculation whether trigeminal neuralgia may not depend partly on the presence of touch sensation. This disturbing observation, if confirmed on subsequent examinations, may raise a more serious objection to intramedullary tractotomy than the occurrence of neurologic complications.

CASE 19.—R. M., a woman aged 51, had major trigeminal neuralgia affecting the first division of the right nerve. Right intramedullary tractotomy was performed in January 1940.

Examination ten days after operation revealed no incoordination in the right arm. There were, however, definite difficulties in walking. The patient lurched and staggered to the right. She also complained of numbness over the ulnar aspect of the right hand.

One month after operation, examination in the follow-up clinic showed very minor disturbances. Her gait was slow and wide based, but there was no staggering. She still complained of a sensation of numbness of the fourth and small fingers and the ulnar aspect of the right hand.

She was seen in the follow-up clinic in June, about six months after operation. A sensation of numbness and tingling was still present in the outer two fingers of the right hand, but this was mild and only occasionally obtruded itself into consciousness. The neurologic examination was entirely normal.

The ophthalmic division of the trigeminal nerve was analgetic, the maxillary division moderately hypalgetic and the mandibular division slightly hypalgetic. There was complete relief from trigeminal neuralgia.

The neurologic disturbances were mild and transitory. This case serves as another demonstration that incisions placed lower in the medulla are less likely to produce neurologic complications. In this case the result was completely satisfactory.

COMMENT

There is plainly a discrepancy between our ¹¹ early experience and that reported by other investigators with respect both to the incidence and to the severity of the neurologic complications following tractotomy. Several factors seem to account for this difference, one of which is simply quantitative—the number of cases in which the operation was performed. Had our experience been limited to cases 2, 4 and 5, in the early series, we should also have received the impression that neurologic complications either did not occur or were unimportant. The value of an operation, however, must be judged not only on the results obtained when the procedure is perfectly performed but on the complications when it is not done precisely, because of minor surgical errors in the placing of the incision, anatomic variations, obscuring by vessels of the surface of the medulla, edema, hemorrhage or other unforeseeable factors. Therefore, the hazards inherent in an operation of this kind can be demonstrated only in large series in which the entire gamut of difficulties has been run.

In every instance we attempted, although in several we failed, to incise deeply enough to produce analgesia of the entire half of the face. While it is possible, of course, to injure contiguous structures without producing facial analgesia, if an incision is badly placed, the likelihood of injury of neighboring nuclei and tracts increases with the effort to transect completely the descending tract. This observation applies particularly when the incision is made at a level opposite the open fourth ventricle, but it may explain the statements of other surgeons who have claimed not to have seen neurologic sequels, for inspection of their protocols suggests that they did not incise quite deeply enough. In Sjöqvist's series, for instance, the neurologic sequels occurred only in cases 4 and 9, which were precisely those in which the most profound sensory defects were produced in the face. In cases 1, 2, 3, 5, 6, 7 and 8 there were no neurologic complications, but neither was complete analgesia produced in the half-face. We think it probable that his failure to secure analgesia and the lack of neurologic complications are both explainable on a common basis, namely, insufficiently deep incisions. In both of Walker's cases incisions were apparently inadequate also, since analgesia was not produced in either case. The same may be said of Rowbottom's second and third cases.

The delusion that neurologic complications do not occur may also have arisen from the fact that the patient is generally kept in bed and not examined on his feet until a week or ten days after operation. Thus, the "uneventfulness" of the postoperative course may be largely an impression gathered from tests only of the upper extremities during this period. As our experience amply demonstrated, various degrees of gait and equilibratory disturbances may exist during the early postoperative course but pass unnoticed unless the patient is examined on his feet.

The duration of the neurologic disturbances is directly related to their postoperative intensity. In only 5 of our early cases was the period of observation sufficiently long to enable us to witness the ultimate outcome; death prevented long term observations on most of the patients suffering from malignant disease. It is our impression, nevertheless, that if the patient had lived long enough, neurologic compensation would have occurred in all cases. This conclusion corresponds to

11. Sjöqvist.² Jackson and Ironside.⁵ Walker.⁶

that of Ferraro and Barrera,¹² who experimentally, in the monkey, destroyed the restiform body and the cuneate nuclei, either separately or in combination.

Shifting of the medullary incision more caudally, as was previously described, greatly decreases the risk of producing serious or persistent neurologic complications, through injury to the restiform body and the cuneate nuclei, but the risk is by no means completely eliminated.

The procedure of tractotomy is just moving out of the experimental stage. The complications reported here must be expected in an operation of so delicate a character; indeed, their occurrence is salutary in that they force the devising of modifications to render the procedure safer and the results surer. Tractotomy has a place in the surgical treatment of facial pain because it offers certain advantages not obtained by the other, classic procedures. However, the results will probably continue to be more capricious than those obtained with the classic procedures. For this reason, the indications for intramedullary tractotomy are limited, and at present the operation is not to be considered as a routine treatment of major trigeminal neuralgia. Its widest usefulness, as we have previously indicated,^{8a} is in the treatment of malignant disease about the face when it is desired to section the glossopharyngeal nerve and the posterior roots of the upper cervical nerves through the same incision.

SUMMARY

As a result of our experience with medullary tractotomy, it has been found that a section in the medulla placed from 6 to 8 mm. caudal to the lower end of the fourth ventricle (obex) will produce satisfactory analgesia of the face, with fewer neurologic sequelae than with the usual methods. That a section at this level produces anesthesia of the face indicates that all three divisions of the fifth nerve are represented in the descending root at this level.

104 South Michigan Avenue, Chicago.

3400 Spruce Street, Philadelphia.

12. Ferraro, A., and Barrera, S. E.: Effects of Experimental Lesions of the Posterior Columns in Macacus Rhesus Monkeys, *Brain* **57**:307, 1934; Summary of Clinical and Anatomic Findings in the Dorsal Column System of Macacus Rhesus Monkeys, *A. Research Nerv. & Ment. Dis., Proc.* **15**:371, 1935; Posterior Column Fibers and Their Terminations in Macacus Rhesus, *J. Comp. Neurol.* **62**:507, 1935; The Effect of Lesions of the Dorsal Spinocerebellar Tract and Corpus Restiforme in the Macacus Rhesus, *Brain* **58**:174, 1935; The Effects of Lesions of the Dorsal Column Nuclei in the Macacus Rhesus, *ibid.* **59**:76, 1936; Effect of Lesions of the Juxtarestiform Body (I. A. K. Bundle) in Macacus Rhesus Monkeys, *Arch. Neurol. & Psychiat.* **35**:13 (Jan.) 1936.

SPINAL NECROSIS AND SOFTENING OF OBSCURE ORIGIN

NECROTIC MYELITIS VERSUS MYELOMALACIA; REVIEW OF LITERATURE AND CLINICOPATHOLOGIC CASE STUDIES

LIEUTENANT DANIEL JAFFE

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

WALTER FREEMAN, M.D., PH.D.

WASHINGTON, D. C.

There are numerous reports in the literature, under varying designations, concerning diseases of the spinal cord of undetermined origin, with softening or necrosis the prominent postmortem feature. The subject has been one of general confusion. No classification has been possible in the face of ignorance of etiologic factors; pathogenesis has been equally uncertain, and the interpretation of pathologic material has produced no uniformity of opinion regarding the nature of the morbid changes. Some investigators have assumed the process to be inflammatory and have applied the term "necrotic myelitis." Others have preferred "myelomalacia," to indicate the degenerative features. Several other descriptive titles have been used. A review of the numerous reports may be helpful in drawing a general picture and in correlating the various opinions which have been advanced.

In 1926, Foix and Alajouanine¹ published a report of 2 cases which they believed represented a new disease entity, subacute necrotic myelitis. Clinically, their cases presented the following picture:

1. Progressive amyotrophic paraplegia, spastic at the start and later flaccid, advancing from below upward, with amyotrophy in the lower segments as the spasticity spread to the upper segments.
2. Sensory impairment, at first dissociated, later complete, with onset after some progress in the paralytic phenomena.
3. Albuminocytologic dissociation of the spinal fluid.
4. Subacute course, with fatal issue in one to two years.

The anatomic observations were quite distinctive in each case. Necrosis in the spinal cord chiefly affected the lumbosacral segments and tended to disappear in the midthoracic segments. The gray matter was involved predominantly, but the white substance was affected as well. The vascular changes were described as "endomesovascularitis," consisting of enormous hypertrophy of the large extramedullary vessels of the cord, the veins being affected more than the arteries. No obliteration of the lumens of the extramedullary or the intramedullary vessels was noted. The changes were distinct from those of syphilitic arteritis, according to the statement of the authors. No etiologic factor was determined in either of the 2 cases described, and it was the opinion expressed by these investigators that some toxic or infectious agent had affected simultaneously the media of the vessels and the parenchyma of the cord.

From the Departments of Neurology, George Washington University and the Gallinger Municipal Hospital.

Read (in part) before the Section on Neurology and Psychiatry of the Medical Society of the District of Columbia, Feb. 5, 1942.

1. Foix, C., and Alajouanine, T.: *La myélite nécrotique subaiguë*, *Rev. neurol.* 2:1 (July) 1926.

TABLE 1.—Cases Reported Under Heading of *Necrotic Myelitis**

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Foix and Alajouanine, 1926	29; male	Albuminuria at 16 years of age, bout of lumbar pain. Onset with progressive intermittent elaudication	Atrophy of leg and thigh muscles. Reflexes active; ankle clonus +; Babinski sign —; sensation intact	Progressive weakness of lower extremities with flaccidity, areflexia and atrophy; dissociated sensory loss to L 5, progressing to complete anesthesia, to Th 12. Intestinal obstruction; pyuria; decubitus; death after 2 yr. and 9 mo.	Xanthochromia; massive hyperalbuminosis; slight lymphocytosis. Wassermann reaction —	Necrosis, maximal in lumbosacral segments; gray matter more predominantly involved than white. "Endomesovascularitis" of extramedullary vessels. Destruction of nerve cells, with demyelinated foci. Meningeal reaction, cells loaded with pigment
	27; male	Albuminuria; lead colic; no symptoms referable to nervous system prior to onset; sudden weakness of legs, progressive for 3 mo.	Paraplegia; knee jerks active; ankle jerks absent; sensory function intact; optic neuritis	Remission 3 mo.; then flaccid paraplegia, areflexia, atrophy and dissociated anesthesia to umbilicus; later complete. Death 11 mo. after onset	Xanthochromia; massive hyperalbuminosis; slight lymphocytosis. Wassermann reaction —	Paraneurmatous and vascular changes similar to those in case 1. Numerous compound granular corpuscles; meningeal lymphocytic infiltration
van Gehuchten, 1927	34; female	Flaccid paraplegia with sensory impairment, ascending to upper extremities, 4 yr. previously, during pregnancy; disturbance cleared completely after 3 to 4 mo. Onset of present illness with delayed menses, headache, nausea; flaccid paraplegia and urinary retention after 48 hr.	Flaccid paralysis of lower extremities; areflexia; sensory loss for all modalities to Th 11	No alteration in neurologic picture. Cystitis; decubitus; downhill course, with intermittent fever; death 3 mo. after onset	Albumin 1,000 mg. per 100 cc.; numerous lymphocytes; (Wassermann reaction of blood —)	Cord much reduced in size from Th 6 down; degeneration of white columns; marked glial reaction; perivascular lymphocytic infiltration; necrosis from Th 10-S 2, with intense destruction, neuroglial proliferation, lymphocytic infiltration and compound granular corpuscles. Hyperplasia of intramedullary and extramedullary vessels; small abscess in posterior column at S 1
Van Bogaert, Ley and Brandes, 1930	20; female	Pain in lower part of back, papular eruption, pains and paresthesia in lower limbs; fever, flaccid paralysis and urinary retention 10 wk. after first symptoms. Insomnia, myoclonic twitchings of abdominal muscles	Flaccid paralysis of lower extremities, with loss of reflexes; muscular atrophy; sensory level to Th 12; root pains from L 1 to S 1; incontinence	Sensory and reflex improvement. After several months, cerebral symptoms: trigeminal pain, headache, insomnia, ataxia, myasthenus, progressive blindness. Cerebral hypertension; decompression, death about 1 yr. after first symptoms	No examination	Necrosis in dorsal portion of cord, especially gray matter. Vascular hyperplasia with dilatation. Changes throughout central nervous system: lymphocytic infiltration; foci of necrosis; glial proliferation; vascular hypertrophy
Lhermitte, Fribourg-Blanc and Kyrle, 1931	50; male	Infectious episode with fever, followed by difficulty in locomotion and uncertainty of gait; no muscular weakness	Hyperreflexia; ankle clonus and Babinski sign bilaterally; absence of abdominal reflexes; sensory diminution to touch and pain almost to umbilicus	Increasing stiffness; spasticity; vesical impairment. Recession of sensory level; dissociation. Slowly progressive course; no muscular wasting. Craniotomy; paralysis; death. Duration 2½ yr.	40 lymphocytes; albumin 1.18 Gm. per 100 cc.; Wassermann reaction —	In dorsal portion of cord, homogenization of tissue, proceeding to cavity formation, rarefaction, gliosis and vascular proliferation
Marinisco and Draganesco, 1932	47; female	Pain in thighs, followed in 2 wk. by pain in neck, shoulders and lower limbs; inability to move legs	Flaccid quadriplegia with hyporeflexia; bilateral Babinski sign; dissociated anesthesia, with indistinct cervical level	Urinary retention; febrile course. Death in 5 wk.	1 cell; Pandy reaction —	Softening and hyperemia of cervical part of cord; necrosis of gray matter; spongy changes in white. Vascular hypertrophy; massive adventitial thickening. No inflammatory infiltration

52; male	Lightning onset, in 24 hr.	Complete flaccid paraplegia with hyporeflexia; dissociated anesthesia to Th 7; urinary retention	Rapidly progressive, febrile course; terminal loss of all sensation in lower extremities. Death 20 days after onset	3 cells; Pandy reaction 1+	Softening, Th 5-9; marked necrosis, Th 6. Vascular involvement, limited to surface vessels at level of destructive lesion. Hyperplasia; lymphocytic infiltration
Minén, 1932	Sudden onset of blindness 5 yr. previously	Complete flaccid paraplegia; tendon jerks preserved but diminished		Yellow fluid, 46 cells; Nonne-Apert reaction +	Necrosis less frank than in previous cases; vascular hypertrophy pronounced
29; male	Generalized erythema following inoculation with anti-tetanus serum; weakness of lower extremities about this time; slowly progressive course	A year after onset, paraplegia, hyperreflexia, bilateral Babinski sign; loss of vibratory sense in lower extremities; difficulty in urination	Progressive sensory and motor impairment, reaching upper extremities in 2 yr.; slow development of flaccidity. Operative exploration; death 2 yr. and 7 mo. after onset	30 lymphocytes; albumin 2 Gm. per 100 cc.; Wassermann reaction doubtful	Encephalomyelitis: In brain, lymphocytic infiltrations, rarefied foci, gliosis, prominent perivascular hemorrhages. In cord, loss of form at C7, spongy debris, marked hyperplasia of central vessels, cavity in sacral region
Zhitomirskaya and Ovcharenko, 1937	Typhus fever during year of onset; beginning of illness with general debility and weakness of legs	Spastic paraplegia; loss of pain sense below Th 10; suppression of urine	Within 4 mo. flaccid paraplegia and atrophy; anesthesia complete to Th 4. Temporary improvement, followed by recurrence, with paralysis and contractures of upper extremities and death within 1 yr. of onset	Normal	Cerebral cortex: degeneration of nerve cells, lymphocytic infiltrations, minute fresh hemorrhages, pale stain subcortex. Spinal cord: foci of necrosis from cervical to lumbar segments, diffuse degeneration of thoracic portion of cord. Hyperplasia of small vessels, lymphocytic infiltrations, destruction of ganglion cells, necrosis most prominent in gray matter
46; male	No past illness known. Onset with pain in right leg; paralysis next day	Flaccid paraplegia; areflexia; complete sensory loss to Th 10; urinary retention	Muscular atrophy in lower extremities; febrile course; death in 10 wk.	White corpuscles 3-5 per field; protein 2.69 Gm. per 100 cc.; Wassermann reaction —	(Acute endocarditis.) Cerebral cortex: degeneration, infiltrations. Spinal cord: necrosis at thoracic level, vascular hyperplasia, glial reaction, nerve cell degeneration, lymphocytic infiltrations, petechial hemorrhages
35; female	Onset sudden, with chill, fever, impaired vision and loss of power in lower limbs	Flaccid paraplegia and areflexia of lower extremities; weakness of upper extremities; anesthesia to Th 5; urinary retention	Headache, nuchal rigidity, nystagmus, optic nerve atrophy; paralysis of hands, anesthesia to Th 3. Slight temporary improvement; death 2½ mo. after onset	Xanthochromia; protein 250 mg. per 100 cc.; 20 white cells per cu. mm.; Pandy reaction strongly +; Wassermann reaction —	Necrosis entire length of cord, maximal in thoracic region; white matter predominantly affected; increase in perivascular spaces; connective tissue formation; lymphocytic infiltrations and altered cells in cerebrum and petechiae in tuber cinereum
47; male	Pains, followed by weakness in lower extremities	Hypotonia; weakness; absence of reflexes in lower extremities; absence of abdominal and cremasteric reflexes; sensory level to Th 12; urinary retention	Course rapidly downhill; decubitus; febrile course; death after 8 wk.	Turbid; 680 cells per cu. mm.; Pandy reaction +++; protein 50 mg. per 100 cc.; Wassermann reaction —	(Carcinoma of stomach; metastases to omentum.) Cord amorphous and necrotic from midthoracic level down; destruction of gray and white matter; meninges heavily infiltrated, chiefly with leukocytes. Vascular hypertrophy, without obliteration of lumen; intimal splitting. Necrosis most marked near thickened vessels
Juba, 1938					

TABLE 1.—Cases Reported Under Heading of *Necrotic Myelitis*—Continued

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Greenfield and Turner, 1939	37; female	Attacks of sciatic pain 5 yr. previously, which cleared after tonsillectomy; intermittent painless swelling of knuckles. Onset with numbness and weakness of right leg, then of left leg; incontinence	Flaccid paralysis, with areflexia of lower extremities; complete sensory loss to Th 10	Sensory level to Th 8; motor weakness of upper abdominal and intercostal muscles. Death with urinary infection 5 wk. after onset	18 cells, chiefly polymorphonuclears; 500 mg. protein per 100 cc.; Wassermann reaction —	Cord softened from Th 8-11 and L4-S; lacunas, collagenous fibers from walls of vessels, frank necrosis; white columns chiefly affected. Small vessels and anterior spinal vein at L3 thickened. Necrosis most marked near thickened vessels
	55; male	Gout; articular fibrillation. Onset with numbness of left leg 7 mo. before admission; 1 mo. later, numbness of right leg and weakness of both lower extremities; urinary difficulty 4 mo. before admission	Weakness, atrophy, hyper-tonus and hyperreflexia of lower extremities; hyperalgesia to Th 9 and total impairment of sensation below knees	Ascent of sensory level to Th 7. Laminectomy; death on 5th post-operative day, 9 mo. after onset	1 cell; protein 100 mg. per 100 cc.; Wassermann reaction —	At Th 11-12, lacunar degeneration and necrosis, particularly of lateral and posterior columns; from Th 8 down thickening of anterior spinal vein; hypertrophy of intramedullary vessels
	61; male	Onset with pain in right leg, pain 3 mo. later in left; weakness after 6 mo.; urinary difficulty in 6½ mo.	Weakness of lower extremities; increased tone, no atrophy. Vibratory and position senses diminished in lower extremities; intact cutaneous sensation; intact	Flaccidity in legs after 3 wk., flexor spasms, muscular atrophy; sensory impairment for all modalities to Th 10 after 2 mo. Death in 12 mo.	(1) 3 cells; protein 70 mg. per 100 cc.; Wassermann reaction — (2) no cells; protein 100 mg. per 100 cc.	Lacunar degeneration and fenestration at Th 8-11; early necrosis of white and gray matter at Th 12; dense gliosis at Th 6, with surface vessels thickened and almost occluded; thickening of intramedullary vessels at Th 12-L2
Draganesu and Lupasu, 1940	43; male	Indisposition (cold) 3 days previously; pain in back and limbs, followed in a few hours by numbness and paralysis of legs; febrile course	Flaccid paralysis of lower extremities; areflexia; weakness of arms; global anesthesia to C5-7; urinary retention; constipation	Total paralysis, including upper limbs; anesthesia to upper cervical segments; respiratory difficulty; dysphagia. Death 5 days after development of paraplegia	Fluid clear; Pandey reaction 3+, cells 2.9; protein 0.44 mg. per 100 cc.; Wassermann reaction —; culture sterile	Destructive process most intense from C3-6; hemorrhagic softening; necrosis without histologic evidence of inflammation
Dansmann, 1940	28; male	Grip and mandibular abscess 5 wk. before admission. Onset with pain in legs; rapid impairment of locomotion	Weakness of lower extremities with hyporeflexia; sensory loss for all modalities to L2	Ascent of sensory level to Th 7 after 1 day; paresthesias of hands; incontinence; decubitus. Death 6 wk. after onset, with ascending urinary infection	(1) 16 cells; protein 4.9 mg. per 100 cc. (normal 0.8-1.3 mg.). (2) 963 cells; protein 16.8 mg. (3) 28 cells; protein 2 mg.; Wassermann reaction —; culture sterile	Chronic, circumscribed caudal meningitis. Lowest segments completely destroyed; meninges thickened, with leukocytic infiltrations. Thoracic segments necrotic, particularly white matter, with circumscribed cellular infiltrations. Cervical segments necrotic, with syringomyelic cavity surrounded by gliosis. Adventitial collaring with lymphocytes

* In this table, and in the accompanying tables, levels in the cord are designated by letters and numerals: L, c., C, Th, L and S indicate cervical, thoracic, lumbar and sacral levels.

After this report, other cases were described under the same title. Some of these were similar to the cases of Foix and Alajouanine; others differed in many respects.

Van Gehuchten² described a case in which the onset was more rapid and the clinical course more acute. Here, the paraplegia developed within forty-eight hours; it was flaccid from the beginning, and no ascent was noted. The sensory loss was complete from the start. The protein content of the spinal fluid was 1,000 mg. per hundred cubic centimeters, and many lymphocytes were noted. The course of the disease was progressive, and death occurred three months after onset. Anatomically, necrosis was pronounced in the lower thoracic segments, involving the white and the gray matter. Vascular hyperplasia and dilatation were present, but not in a degree comparable to that seen in the original cases. Lymphocytic infiltrations were noted in some places, and in the first sacral segment a small abscess appeared. Van Gehuchten expressed the opinion that the necrotizing character of the disease did not speak for a specific etiologic factor and that a single infectious agent might produce various types of myelitis—infiltrative or degenerative, acute or subacute, with or without necrosis—depending on the degree of virulence. He postulated that many of the special forms of myelitis that have been described may all be referable to the same etiologic factor.

The next report to appear under the original designation was that of van Bogaert, Ley and Brandes.³ These authors recorded a case with paraplegia which cleared after an acute onset, followed six months later by cerebral complications. Death followed operation for decompression. Anatomically, degenerative changes were noted, particularly in the thoracic portion of the cord, and were accompanied by vascular hyperplasia with dilatation. Throughout the central nervous system, however, there were abnormal foci, with lymphocytic infiltration, vascular hypertrophy, glia proliferation, cellular degeneration and necrosis.

Lhermitte, Fribourg-Blanc and Kyriaco⁴ described a case in which the illness was of two and a half years' duration, with slowly progressive spastic paraplegia, which remained spastic until death, and without muscular wasting. Sensory loss was first dissociated and later complete, but without ascent of the level. Examination of the spinal fluid showed marked increase in protein and 40 lymphocytes per cubic millimeter. Postmortem examination revealed changes in the thoracic portion of the spinal cord, consisting of gliosis, vascular proliferation, rarefaction, homogenization of the parenchyma and cavity formation.

The following year Marinesco and Draganesco⁵ reported 2 cases in which a more acute picture was presented. The clinical features included lightning onset of an acute febrile illness with flaccid paralysis and hyporeflexia, dissociated sensory loss (later complete in 1 case) and urinary retention. The cell and protein contents of the spinal fluid were normal in the first case, while in the second case there were 3 cells per cubic millimeter of fluid and a positive Pandy reaction. Death occurred after five and three weeks respectively. Necrosis was seen between the fifth to the eighth cervical segment in the first case and at the sixth thoracic segment in the second. The white and gray matter were involved in both instances,

2. van Gehuchten, P.: Un cas de myélite nécrotique aiguë, *Rev. neurol.* 1:505 (April) 1927.

3. van Bogaert, L.; Ley, R. A., and Brandes, F.: Contribution anatomo-clinique à l'étude de la myélite nécrotique subaiguë de Foix-Alajouanine, *Rev. neurol.* 2:1 (July) 1930.

4. Lhermitte, J.; Fribourg-Blanc, and Kyriaco, N.: La gliose angéio-hypertrophique de la moelle épinière (Myélite nécrotique de Foix-Alajouanine), *Rev. neurol.* 2:37 (July) 1931.

5. Marinesco, G., and Draganesco, S.: Myélite nécrotique aiguë, *Ann. de méd.* 31:5 (Jan.) 1932.

and vascular hyperplasia was particularly striking at the level of the lesions. In the first case no inflammatory changes were noted; in the second there were prominent lymphocytic infiltrations, especially about the veins, in the necrotic areas. These authors expressed the belief that the rapidity of the process in their cases, as well as in that of van Gehuchten, accounted for the less pronounced degree of vascular hyperplasia as compared with the hypertrophic changes described by Foix and Alajouanine. They pointed out, too, that the necrotic character of the parenchyma was not a specific feature, having been described in certain cases of herpes zoster, experimental encephalomyelitis, neuromyelitis optica and acute multiple sclerosis.

Minéa⁶ reported a case with paraplegia, in which sudden onset of blindness had occurred five years previously. Anatomically, the spinal cord was the seat of degeneration, with somewhat less frank evidence of necrosis than that observed in the cases described previously. Vascular hypertrophy was outstanding.

Riser, Geraud and Planques⁷ described a case of "subacute necrotic encephalomyelitis." Motor and sensory impairment extended to the upper extremities from a previous level at the sixth thoracic segment. The pathologic changes were those of necrotizing encephalomyelitis. In the cerebrum there were lymphocytic infiltrations, foci of rarefaction, gliosis, vascular occlusion and some perivascular hemorrhages. The spinal cord was noticeably softened and spongy at the seventh cervical segment.

Zhitomirskaya and Ovcharenko⁸ recorded 3 cases, in the first of which the condition resembled the syndrome described by Foix and Alajouanine. Onset followed an attack of typhus fever. In the second and third cases the disease was of shorter duration, with a clinical course similar to that noted in van Gehuchten's case. In the second case acute bacterial endocarditis was present, and the possibility of embolic phenomena in the spinal cord must be considered. In the third case there were visual complications, and the condition was suggestive of neuromyelitis optica with involvement of the cord progressing to necrosis. These authors suggested that the clinical picture of flaccid paralysis and total anesthesia occurred as the result of involvement of the white matter of the cord in cases of so-called acute necrotic myelitis, whereas spastic paralysis and dissociated anesthesia could be correlated with lesions in the gray matter in cases of subacute necrotic myelitis.

Juba⁹ described a case presenting the acute picture, with flaccid paralysis of the lower extremities and complete sensory loss to the twelfth thoracic segment. Postmortem examination revealed carcinoma of the greater curvature of the stomach and necrosis of the spinal cord, most pronounced in the midthoracic region.

Greenfield and Turner¹⁰ reported 3 cases representing both the acute and the subacute type. They described three stages in the tissue alterations leading to necrosis, namely lacunar degeneration, mesodermal reaction and, finally, frank necrosis. These authors expressed the belief that the parenchymal lesions were wholly dependent on disease of the vessels and that the involvement of the intra-

6. Minéa, I.: Cas de myélite subaiguë d'origine infectieuse cryptogénétique, *Bull. Soc. roumaine de neurol., psychiat., psychol. et endocrinol.* **13**:27, 1932.

7. Riser, Geraud, and Planques: De l'encéphalomyélite nécrotique subaiguë, *Rev. neurol.* **67**:455 (April) 1937.

8. Zhitomirskaya, B. M., and Ovcharenko, E. P.: Concerning Necrotic Myelitis, *Sovet. psikhonevrol.* **13**:59, 1937.

9. Juba, A.: Myelitis necroticans subacuta (Foix-Alajouanine), *Deutsche Ztschr. f. Nervenhe.* **148**:17 (Nov.) 1938.

10. Greenfield, J. G., and Turner, J. W. A.: Acute and Subacute Necrotic Myelitis, *Brain* **62**:227 (Sept.) 1939.

medullary vessels noted in cases of the acute type preceded that of the large surface vessels, the degeneration of which was prominent in cases of the subacute and chronic forms.

Draganescu and Lupascu¹¹ described the syndrome of Landry's ascending paralysis occurring in the course of acute necrotic myelitis.

In the same year (1940) Dansmann¹² recorded a case in which grip and mandibular abscess preceded the onset of symptoms of involvement of the spinal cord. The course was rapidly progressive, with death in six weeks. There was circumscribed chronic meningitis in the caudal segments, with complete destruction of the parenchyma of the cord. Necrotic foci were described as high as the cervical segments. The author concluded that the process had resulted from vascular dissemination of a bacterial infection and stated it was likely that a toxin rather than the organisms themselves caused the spinal lesions.

In this country, the term "necrotic myelitis" has been avoided. Moersch and Kernohan¹³ recorded 3 cases under the title "progressive necrosis of the spinal cord," and Schunk and Kernohan¹⁴ later added a case of similar nature with cerebral involvement.

In a discussion on the paper by Moersch and Kernohan,¹³ before the American Neurological Association, Hassin stated that the condition under consideration is usually classified with the myelomalacias and that the cause is usually vascular (thrombosis or embolism), but that an infectious agent might produce a similar effect. Moersch and Kernohan maintained that the process was probably due to the action of some virus or toxin and should have a designation distinct from the myelomalacias, which are due to "purely vascular or so-called degenerative changes."

Moersch and Kernohan indicated the similarity between their cases and those of Foix and Alajouanine but pointed out that vascular changes were prominent in the French cases, while in their own, vascular hyperplasia appeared only in the first, and then involved the walls of the smaller vessels.

The reports of 6 earlier cases were reviewed by Moersch and Kernohan as representative of "progressive necrosis of the spinal cord." Most of these had been described under the heading of myelomalacia by Basso and Hassin,¹⁵ Schmitt,¹⁶ d'Antona,¹⁷ Low¹⁸ and Stone.¹⁹ Feindel²⁰ had recorded his case as one of acute ascending necrosis of the spinal cord. The cases of Nonne,²¹ Davison and

11. Draganescu, S., and Lupascu, G.: Sindrom de paralizie ascendenta de tip landry in cursul unei mielite necrotice acute, *Rev. stiint. med.* **29**:210 (March) 1940.

12. Dansmann, W.: Ueber die sogenannte Myelitis necroticans subacuta, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **168**:644, 1940.

13. Moersch, F. P., and Kernohan, J. W.: Progressive Necrosis of the Spinal Cord, *Arch. Neurol. & Psychiat.* **31**:504 (March) 1934.

14. Schunk, P., and Kernohan, J. W.: Progressive Necrosis of the Spinal Cord, with Cerebral Involvement, *Rocky Mountain M. J.* **36**:789 (Nov.) 1939.

15. Basso, P., and Hassin, G. B.: Myelitis and Myelomalacia, *Arch. Neurol. & Psychiat.* **6**:32 (July) 1921.

16. Schmitt, W.: Ueber akute Rückenmarkserweichung (Myelomalacie), *Deutsche Ztschr. f. Nervenhe.* **72**:78 (Jan.) 1921.

17. d'Antona, S.: Sulla necrosi spinale acuta nel corso dei tumori maligni, con un contributo alla conoscenza delle "ernie spinali malaciche," *Neurologica* **3**:65 (April) 1926.

18. Low, A. A.: Acute Ascending Myelomalacia, with Clinical Picture of Landry's Paralysis: Clinicopathologic Report of Case, *Arch. Neurol. & Psychiat.* **21**:594 (March) 1929.

19. Stone, T. T.: Myelomalacia, *Arch. Neurol. & Psychiat.* **21**:718 (March) 1929.

20. Feindel, R.: Ueber akute aufsteigende Rückenmarksnekrose, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **68**:147 (July) 1921.

21. Nonne, M.: Myelodegeneratio transversa carcino-toxaemica, *Med. Klin.* **2**:943, 1919.

TABLE 2.—Cases Classified by Moersch and Kernohan Under Heading of Progressive Necrosis of the Spinal Cord

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Nonne, 1919	65; male	Old chronic cough; clinical duodenal ulcer. Two weeks' history of weakness of legs and urinary retention	Weakness of lower extremities, diminished reflexes; sensory diminution for all modalities to umbilicus; sphincter paralysis	Total paralysis and complete anesthesia to umbilicus, after temporary remission; death 2 mo. after onset of spinal symptoms	Xanthochromia; globulin +++; no lymphocytes	(Careinoma: lungs, hilar nodes, thyroid, retroperitoneal glands and vertebral bodies Th 8-12; no destruction of vertebrae; interspaces normal; no metastases to meninges or cord.) Cord softened in thoracic region; degeneration of nerve fibers and myelin sheaths, with failure to take stain; many phagocytic cells; vessels increased in number and thickened
Bassoe and Hassin, 1921	45; female	Sore throat 7 wk. previously. Onset with weakness of lower extremities; febrile course	Motor and sensory impairment of lower extremities; hyperreflexia; pallor of right optic disk	Progress of motor and sensory impairment to level of 4th rib; flaccidity of extremities in 2 days; disappearance of tendon jerks in lower extremities; death after 5 mo.	26 cells; globulin ++; Wassermann reaction weakly +, later —; gold curve 4333211100	Thoracic portion of cord semifluid; cavity formation; demyelination; gutter cell infiltration; glial reaction; no inflammation
Feindel, 1921	23; male	Amputation of left leg at mid thigh few months previously; radiotherapy. Two injections of arsphenamine with no reaction at time	Fever; flaccid paralysis of lower extremities; ascent of motor and sensory level to arms	Respiratory paralysis; death 3 wk. after onset	No examination	Lumbar and thoracic portions of cord swollen and reddish; demyelination; gutter cell infiltration; no inflammatory reaction; vessels not remarkable
Schmitt, 1921	17; male	Infection of tongue 1 mo. previously. Onset with weakness of left leg	Weakness, more in left lower extremities; spasticity, ataxia, hyperreflexia on left side, with Babinski sign	Motor and sensory loss to waist; deep reflexes of lower extremities absent; flaccidity on 3d day. Pains in arms and chest; death in 8 wk.	(1) 14 cells; globulin 1+; Wassermann reaction —. (2) Yellow fluid; cells 1,052	Marked softening; degeneration maximal from Th 4 to L 1; other regions of degeneration from O 5 to lumbar; no inflammatory changes
d'Antona, 1926	41; male	Adenocarcinoma of lung (metastases to ribs and liver). Sudden onset of paralysis of lower extremities; urinary retention	Motor and sensory paralysis to umbilicus, with diminution of deep reflexes	Ascent of motor and sensory loss to nipple line. Rapidly downhill; death after 8 wk.	Yellow fluid; many erythrocytes, polymorphonuclears, a few lymphocytes; globulin 1+; protein 60 mg. per 100 cc.; Wassermann reaction —	Cord gelatinous, herniated; many small nodules from Th 5 to L 3; pronounced necrosis; no inflammation
Low, 1929	30; female	Induced abortion few weeks prior to onset. Severe pain in lower extremities; numbness; paralysis	Flaccid paraplegia, with loss of reflexes in lower extremities; complete sensory loss to Th 10; fever	Ascent of sensory loss to clavicles in 1 mo.; death with respiratory difficulty in 9th wk.	338 cells; globulin 1+; Wassermann reaction —	Softening of lower thoracic, lumbar and sacral segments; no thrombosis; moderate lymphocytic infiltrations; marked perivascular infiltrations in cervical region; cord creamy and cavitated in softened areas

			Death in 6 wk., with ascending syndrome	Normal	Areas of softening from cervical to lumbar region; gutter cells numerous; no thrombosis or inflammation; glial proliferation; capillary increase
Stone, 1929	26; female	One wk. after attack of influenza, pain in legs; 3 wk. later, paralysis of left, then right, lower extremity, with ascent to upper extremities	Flaccid tetraplegia; loss of deep reflexes in lower extremities; sensory loss to clavicles, complete to umbilicus		
Davison and Keschner, 1933	28; male	Onset with sensation of cold in left leg and delayed thermal perception in both legs; urinary incontinence 9 wk. later	Complete paraplegia of upper neuron type; ataxic tremor and atrophy of muscles of hand, especially on right; loss of all forms of sensation below Th 2. Ptosis, nystagmus, anisocoria, corneal hypesthesia, deviation of uvula	Pressure increased; 70 cells per cu. mm.; globulin 3+; Wassermann reaction —	Cord softened above lumbar and below cervical enlargement; thoracic portion only a shell; cavitations; numerous compound granular corpuscles about vessels; no lymphocytes
Moersch and Kernohan, 1934	37; male	Tightness; pain in legs; numbness below knees. Next day patient unable to move legs, incontinent	Complete sensory and motor loss to Th 12. Tendon reflexes absent; lower abdominal reflexes absent; upper abdominal reflexes present	(1) Numerous red blood cells. (2) Yellow fluid; 235 white cells; protein 60 mg. per 100 cc.; globulin 1+; Kolmer reaction —	Cord soft, completely necrotic in lumbar region; demyelination; some destruction of axis-cylinders; slight inflammatory reaction; moderate scavenger cell reaction; no glia. Cord herniated in some places
	28; female	Recurring tonsillitis. Onset with numbness in feet; coldness and weakness. In 5 days paralysis to waist	Flaccid paralysis and complete anesthesia to Th 7; loss of reflexes; pallor of left optic disk	(1) 11 lymphocytes; globulin 1+; partial block; Kolmer reaction —	Cord soft from C 5 to Th 12; normal markings obliterated; marked necrosis of white matter, less of gray; degeneration of myelin and axis-cylinders. Scavenger cells numerous; inflammation absent; central canal dilated
	17; female	Burn on back failing to heal; squamous cell carcinoma; abscess of breast. Onset with pain in right arm and thorax; next day numbness from hip to knee, then inability to move legs	Paralysis and sensory loss to Th 4 on 4th day; impairment of bladder and bowel controls. Reflexes not noted	8 cells (6 lymphocytes); protein 160 mg. per 100 cc.; globulin +; colloidal gold curve 41433332; Kolmer reaction —; culture sterile	Profound necrosis of entire cord below thoracic segments (not examined above); no metastases; destruction of myelin and fragmentation of axis-cylinders; surface of cord nodular, with herniations; no reaction of any kind
Schunk and Kernohan, 1939	38; male	Onset with weakness and numbness of left leg, rapidly progressing to paralysis of all extremities in course of 4 days	Paralysis of all extremities; hyperreflexia; clonus; bilateral Babinski sign; sensation diminished generally	10 cells, Pandey reaction 1+	Lumbar portion of cord swollen, dark, softened, hemorrhagic and semifluid; thoracic portion soft. No cellular reaction; cord completely necrotic; vessels dilated. In brain, many foci of softening, limited to white matter

Keschner²² and Winkelman and Eckel²³ were mentioned as falling possibly under the same classification.

In Nonne's case softening of the spinal cord appeared to have developed as the result of toxic absorption from a nearby malignant tumor. The occurrence of spinal softening or necrosis in cases with malignant tumors elsewhere will be discussed later.

The case described by Winkelman and Eckel was one of myelomalacia secondary to impaired vascular supply, possibly the result of syphilitic endarteritis. It may be excluded from the group under consideration. Details of the other cases are given in table 2.

A search of the literature has revealed several additional scattered case reports, which are similar in many respects to those already noted. Collins²⁴ described 2 cases in which the origin was obscure and there was pronounced destruction of the cervical segments. Harbitz²⁵ recorded a case in which the disease apparently complicated influenza. Borromeo's²⁶ case was reported as one of degenerative transverse myelitis, and Behr and Wuite²⁷ diagnosed the condition in their cases as "ascending transverse myelitis." The case described by Spiegel²⁸ was unique in that the disease occurred in a 3 year old child. The cases of Melikov²⁹ and Aksel and Kirçak³⁰ may be included in this group. In the case recorded by Silbermann³¹ there were a number of possible etiologic factors, namely, parental syphilis, trauma and an anginal infection. Frymire³² and Stone and Roback³³ reported cases in which the onset followed lifting of heavy weights or back strain. Markiewicz³⁴ cited the case of Neel³⁵ in his discussion of colloidal degeneration in the nervous system. He described the process of "colloidal degeneration," noted in a number of diseases of the nervous system, as the counterpart of amyloid degeneration in other organs. He asserted that vascular changes precede parenchymatous degeneration of a similar nature and that there occurs a spread of some toxic substance from the blood vessels. The process was differentiated from that

22. Davison, C., and Keschner, M.: Myelitic and Myelopathic Lesions: Clinicopathologic Study, *Arch. Neurol. & Psychiat.* **29**:600 (March) 1933.

23. Winkelman, N. W., and Eckel, J. L.: Focal Lesions of the Spinal Cord Due to Vascular Disease, *J. A. M. A.* **99**:1919 (Dec. 3) 1932.

24. Collins, J.: Acute Myelitis and Thrombotic Softening of the Spinal Cord, *Rev. Neurol. & Psychiat.* **10**:159, 1912.

25. Harbitz, F.: Patologisk-anatomiske erfaringer ved influenza og dens komplikationer, *Norsk mag. f. lægevidensk.* **81**:46 (Jan.) 1920; cited by Bassoe, P.: *Nervous and Mental Diseases, Practical Medicine Series*, Chicago, Year Book Publishers, Inc., 1920, p. 20.

26. Borromeo, G.: Su di un caso di mielite trasversa degenerativa a decorso subcronico, *Policlinico (sez. prat.)* **38**:295 (March 2) 1931.

27. Behr, E., and Wuite, J.: Myelitis transversa ascendens, *Acta psychiat. et neurol.* **10**: 657, 1935.

28. Spiegel, H. A.: Myelomalacia in a Three Year Old Child, *Arch. Pediat.* **53**:500 (July) 1936.

29. Melikov, M. M.: Pathogenesis and Pathologic Anatomy of Ascending Myelomalacia, *Sovet. psikhonevrol.* **13**:52, 1937.

30. Aksel, I., and Kirçak, V.: Les myélites de nature inconnue, *Arch. balkan. med. chir.* **1**:27, 1939.

31. Silbermann, J.: Ueber einen besonders schweren Fall von infektiös-toxischer Myelitis mit weitgehender Zerstörung des Rückenmarks, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **116**: 140, 1928.

32. Frymire, W. A.: Acute Spinal Cord Degeneration with a Case Report, *Illinois M. J.* **61**:439 (May) 1932.

33. Stone, L., and Roback, H. N.: Myelomalacia Without Thrombosis Following Indirect Trauma (Strain), *J. A. M. A.* **108**:1698 (May 15) 1937.

34. Markiewicz, T.: Zur Frage der "kolloiden" Degeneration und ähnlicher Vorgänge in Zentralnervensystem, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **159**:53, 1937.

35. Neel, A. W.: Die Bedeutung der Eiweissvermehrung ohne gleichzeitige entsprechende Zellvermehrung in der Spinalflüssigkeit, *Deutsche Ztschr. f. Nervenhe.* **117-119**:309, 1931.

of coagulation necrosis, described by Markiewicz,³⁶ although foci of necrosis did occur, with spongy changes, deposition of "colloidal" particles and "foam cell-like structure" of the endothelium of the smaller vessels.

The cases of morbid softening of the spinal cord reported by Gleckler³⁷ were not accompanied by clinical descriptions and cannot be considered in this series.

Table 3 presents a summary of the details in the aforementioned cases.

Prior to discussion of several of the features included in this review, 4 additional cases, with postmortem studies, may be described.

REPORT OF CASES

CASE 1.—History.—L. J., a Negress aged 42, was admitted to the hospital on Sept. 26, 1940. She dated the onset of her illness to July 1940, at which time she had severe constipation for one week. The left leg became weak at that time, and for a month she got around with a cane. Weakness of the left arm appeared shortly after the onset, with a great deal of pain across the left shoulder and over the extensor surface of the arm and hand. The arm became flexed and clawlike. About a month after the onset the right leg began to weaken, but was without pain. She began to note twitching and tremors in the legs, which would "draw up" involuntarily. Sore throat and some difficulty in swallowing appeared. Three weeks before admission she was compelled to stay in bed because of weakness in the lower extremities. Constipation became persistent, and urgency of urination appeared.

The past history included sinusitis three years prior to admission and hypertension known to have been present for six years.

Examination.—On admission the temperature was 98 F., the pulse rate 78 and the respiratory rate 18. The blood pressure was 150 systolic and 95 diastolic. The cranial nerves were not remarkable except for vertical and horizontal nystagmus and conduction deafness of the right ear.

The lower extremities were spastic, with atrophy of all muscle groups, and only slight motion was present. The upper extremities were weak bilaterally, the left more than the right. The left forearm was held in flexion, with the hand flexed and spastic. There was significant atrophy of the intrinsic muscles of the hand, as well as those of the arm and forearm. There was marked resistance to passive motion, with considerable pain. The reflexes were hyperactive in the upper and lower extremities; the Hoffmann sign was positive and the Mayer reflex negative bilaterally; ankle and patellar clonus and the Babinski sign were elicited bilaterally. The abdominal reflexes were absent. Sensory changes consisted of an increased threshold for position sense in both hands and in the toes; otherwise no impairment was noted.

Lumbar puncture revealed clear, colorless fluid under normal pressure. The manometric readings were normal. There were 20 cells per cubic millimeter, with lymphocytes predominating, and the total protein measured 175 mg. per hundred cubic centimeters.

Course.—On October 6, about ten days after admission, reexamination revealed that the picture had changed to one of profound hypotonia below the waist. Voluntary power in the legs was completely gone, and the patient was totally incontinent. The upper extremities were unchanged. Sensory examination at this time revealed hypesthesia, hypalgesia and thermanesthesia below the eighth cervical segment, with loss of deep sensation from the sixth thoracic segment down. Saddle anesthesia was complete, and a sweating level was noted at the fifth thoracic segment.

Lumbar puncture now revealed albuminocytologic dissociation, with a positive Pandy reaction, a total protein content of 100 mg. per hundred cubic centimeters and 3 cells per cubic millimeter, 2 of which were lymphocytes and 1 a polymorphonuclear leukocyte. The Kahn reaction of the spinal fluid was negative, and the colloidal gold curve was 4332211100.

On October 16 mass reflexes appeared, and there was loss of tendon reflexes in the lower extremities. A spiking temperature was noted on October 20, as the result of an ascending infection of the urinary tract, and at this time examination revealed atrophy of

36. Markiewicz, T.: Zur Frage der "Koagulationsnekrose" im Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **159**:27, 1937.

37. Gleckler, H. E.: Two Cases of Morbid Softening of the Spinal Cord, Odessa M. J. **2**:337, 1927.

TABLE 3.—*Additional Cases from Literature Similar to Those Listed in Tables 1 and 2*

Author and Date	Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
Collins, 1912	29; female	Four mo. previously, transient blindness and pain in face. Onset with paresthesias of extremities; pain and difficulty in walking a week later	After 2 wk. tetraplegia, flaccid in upper extremities; ankle clonus and bilateral Babinski sign; reflexes present in lower and absent in upper extremities; sensory loss in all extremities; hyposthesia to 5th rib; urinary retention	Signs of upward extension; laminectomy performed; death 5 wk. after onset of spinal symptoms	Lymphocytes increased; Wassermann reaction —	(Limited to cervical segments of cord.) O 3 to C 6: extensive softening; hemorrhages; vessels engorged; heavy cellular infiltrations; fatty granular corpuscles, erythrocytes and products; vessels not remarkably altered
	38; female	One week after childbirth, pain in small of back; urinary retention; obstipation; numbness and weakness of lower extremities	Weakness of all extremities; tendon reflexes present, later exaggerated in lower limbs, with Babinski sign and clonus; abdominal reflexes absent on right; complete anesthetesia below clavicles	Anesthesia above clavicles; difficulty in deglutition and respiration; complete paralysis of extremities; absence of knee jerks. Death following laminectomy 2 mo. after onset	No increase in cells	(Limited to cervical cord.) Cord soft, pulpy, shapeless; white and gray matter destroyed. Blood vessels infiltrated. Numerous cellular accumulations; gutter cells; glial overgrowth; neural elements degenerated
Harbitz, 1920	52; female	Influenza, followed by headache and papillitis; blindness in 2 wk.; pain and sensory diminution in both legs	Weakness of trunk and extremities; anesthetesia below axilla	Death 2 mo. after onset	Spinal cord softened in upper third, grayish red, edematous. Marked degeneration, maximal at Th 1, no inflammation
Silbermann, 1928	21; male	Father tabetic; injury to back, with apparent recovery, followed in a week by gingivitis, angina and fever. A week later, sudden onset of weakness, spreading to both legs, with complete sensory loss to knees. Ascent of anesthetesia	12 hr. after onset flaccid paralysis of lower extremities and weakness of neck and trunk; sensory loss to cervical region; paralysis of bladder and bowel	Recession of sensory and motor loss to Th 8 in 6 wk.; transient faecal palsy; downhill course; muscular atrophies; decubitus; death 1½ yr. after onset	Normal	No recognizable structure of cord below Th 9; necrosis, cavitation, demyelination; peripheral gliosis; marked accumulations of fatty granular corpuscles; small vessels hypertrophied
Borronero, 1931	18; male	Onset with pain and paresthesias in lower limbs, followed by ataxia and difficulty in locomotion	Weakness of lower extremities; atrophy of calf muscles; ankle jerks absent; ataxia; Babinski sign absent; thermoaesthetesia over area S 2-S 3	4th month: complete flaccid paraplegia, areflexia, sensory loss S 1-S 2; partial in L 5; later complete sensory and motor loss to groin. Septile course; bed sores; death in 7th mo.	Slight xanthochromia; 20 cells (lymphocytes); Pandy reaction 4+; Wassermann reaction —	Cord gelatinous from lower dorsal portion down. Complete destruction of all elements. Vessels unaltered except for obliterative thromboangitis of a single arteriole
Frymire, 1932	37; male	Onset of weakness and numbness of left leg shortly after lifting of heavy weight; pain in back	After 1 wk., flaccid paraplegia, areflexia, sensory loss to Th 9	Febrile course; toxemia; decubitus; death 2 wk. after first examination	Fluid cloudy; numerous cells; protein content not recorded	Softening of cord at Th 9 to Th 10; substance exuded on opening of dura. Dropping out of white columns. In other regions, nerve degeneration and formation of fat granules

Behr and Wuite, 1935	12; male	Patient fell on pointed object 3 mo. prior to onset; pain disappeared after 1 day. Onset with ataxia, difficulty in walking, pain in back	Flaccid paralysis of lower limbs; areflexia; sensory loss in lower limbs, later reaching nipple line	Ascent of sensory loss to upper extremities, with flaccid paralysis and complete sensory loss; death with respiratory diffi- culty on 7th day	Yellow; numerous polymorphonu- clears; Pandey reaction ++	Cord pulpy, shapeless. Lumbar meninges thick with leukocytes; perivascular infiltrations. Hemor- rhagic exudate. Parenchymal cavi- tation; demyelination; degenera- tion of ganglion cells. Reactive glial changes. Structure of cervical and thoracic segments better preserved
	35; male	Pain in back, numbness; later weakness of legs. Sen- sory loss to umbilicus; uri- nary difficulty; febrile course	Complete paraplegia with loss of reflexes; sensory loss to xiphoid cartilage; urinary retention; nuchal rigidity	Ascent of sensory level to C8; crisis; return of temperature to normal and recession of sensory level to Th 4 or 5. Muscular atrophy, stationary for few weeks. Urinary infection; decubitus; death in 7th mo.	(1) Slightly turbid; pressure elevated; 15,000 cells (poly- morphonuclears; few red blood cells); Pandey reaction ++; (2) Decrease in pres- sure, turbidity, cells and protein	Complete softening of cord from Th 4 down; partial softening as high as C5. Hemorrhagic foci; compound granular corpuscles; reactive gliosis; lymphocytic infiltrations; degeneration of myelin
Spigel, 1936	3; female (colored)	Onset at age of 2½ yr. with backache, then pain in right knee and difficulty in walk- ing. Papular urticaria; swelling of extremities	Flaccid paralysis and atrophy of muscles of back and extremities; inability to support head. Areflexia; no response to pinprick any- where. Passive motion painful	Paralysis of respiration and degh- nition. Febrile course; terminal pneumonia; death 3 wk. after admission	Fluid clear, colorless. No cells; protein normal, smears and culture negative	Thoracic portion of cord most affected; areas of degeneration; cavitation of gray matter. Vaeuo- lation of white matter at other levels; cavities filled with necrotic material; no leukocytes
Melikov, 1937	30; male	Recent attack of malaria; grip just preceding onset. Pain in lower limbs; 4 days later complete paralysis of legs	Complete paralysis of lower extremities; hypertonous. Hyperreflexia of upper and lower limbs; Babinski sign bilaterally; anesthesia to Th 9; urinary retention; slight weakness of left side of face	Ascent of sensory level to C8; paralysis of upper extremities. Tonus in low extremities diminished. Reflexes first hyperactive, later diminished. Nuchal rigidity; respi- ratory paralysis; death in 3 wk.	(1) Fluid turbid; 13 cells; Pandey reac- tion ++; (2) Cloudy, leukocytes. Pandey reaction ++++	(Pleural effusion on right side; atelectasis.) Spinal meninges agglutinated by exudate. Lower thoracic and upper cervical seg- ments disintegrated. Minute hem- orrhages; little inflammatory reaction
Stone and Reback, 1937	31; female	Injury to right arm in fall 4 mo. previously; atrophy of small muscles of hand. "Head cold"; backache on day before onset. Patient pulled herself up on a tree; sudden numb- ness of right leg	Flaccid paralysis of lower and weakness of upper ex- tremities ("cervical cord position"). Reflexes slug- gish in lower and hyper- active in upper extremities; abdominal reflexes absent. Sensory level complete to C8 to Th 1; urinary reten- tion; febrile course	Recession of sensory level to Th 3; slight spasticity in lower extremi- ties; improved motion but atrophy in upper extremities. Decubitis; toxicity; death after 10 mo.	(1) 2 cells; Pandey reaction —; protein 23 mg. per 100 Cc. (2) Erythrocytes. (3) Manometric block. (4) After 3 mo. fluid clear; no block; Pandey reaction —	(Spinal cord only.) softening from C6 to Th 2; cord shrunken, shell- like; meninges thick. Gliosis, gitter cells and small perivascular infiltrations with lymphocytes. Ves- sels collapsed; intimal and adventi- tial proliferation
Aksel and Kireak, 1939	21; male	Onset 1 mo. earlier, with lum- bar pain, numbness over right half of body and later left half. Weakness; incontinence	Flaccid paraplegia, are- flexia, anesthesia; upper extremities hypotonic. Anes- thesia of trunk from costal margin to umbilicus, and hypesthesia posteriorly below Th 10. Absence of abdom- inal and cremasteric reflexes	Urinary infection; death 6 wk. after onset	Normal	Demyelinated foci, not delimited. Lesions in gray matter and about central canal. New vessels formed; cells about vessels filled with lipoid. Neuroglial proliferation; ganglion cells intact; inflamma- tion minimal

the intrinsic muscles of the right hand and forearm. Decubitus ulcers appeared over the sacrum. The skin over the thorax and neck became tough, dry and scaly. Light stroking over the left arm caused exquisite pain. Terminally, there developed trismus and rigidity of all extremities, including the previously flaccid legs. Death occurred on December 17.

Necropsy.—The significant systemic observations were bronchopneumonia, cystitis and pyelonephritis.

On palpation the lower cervical region of the spinal cord appeared softened, with bluish discoloration of its surface. Section after fixation revealed marked destruction in this portion of the cord, with extensive softening and fissuring. The sectioned surfaces appeared yellowish translucent in some areas and whitish opaque in others. These changes extended downward through the upper thoracic segments.

Microscopic preparations revealed widespread destruction throughout the cervical portion of the cord, particularly on the left side. The gray and the white substance were equally involved, with complete disruption of the structure of the cord. The white columns appeared spongy, as the result of formation of lacunas where the myelin sheaths had been destroyed. Numerous areas of cavitation were noted. In many areas mesodermal elements appeared, in



Fig. 1 (case 1).—Destruction of white and gray matter in the cervical segment, particularly on the left side. Weigert stain; $\times 8.5$.

the form of collagenous fibers, particularly about hyperplastic blood vessels. In the regions showing more complete destruction there were acellular and homogeneously stained areas, with infiltrations of lymphocytes, a few polymorphonuclear leukocytes and many macrophages. (The changes in this region corresponded to those described by Greenfield and Turner¹⁰ as lacunar degeneration, mesodermal reaction and frank necrosis.)

On the left side the ganglion cells of the gray horns were almost completely destroyed. On the right side the ventral horn cells were fairly numerous, with moderately advanced degeneration in the form of chromatolysis and pyknosis.

The blood vessels were extremely hyperplastic. The intima and media were chiefly involved, particularly in the large extramedullary vessels in the cervical segments. Here the media presented a thickened lamellation, suggestive of the "onion skin" appearance described by Foix and Alajouanine, but to a lesser degree. Within the substance of the cord at these levels, all of the small vessels showed pronounced hypertrophy, with thickened intima and narrowed lumen. Vascular packets, with small branching, hypertrophic vessels, were seen in some regions. Numerous fat-containing granular corpuscles were noted.

At the other level degenerative changes were less advanced. Secondary degeneration was seen, particularly in the lateral columns. Vascular hyperplasia was limited more strikingly to the smaller vessels. Degenerative reaction was widespread among the ganglion cells. There were no significant changes in the brain or the brain stem.



Fig. 2 (case 1).—Hyperplasia of the large extramedullary vessels of the cervical region, suggestive of "onion peel appearance." Hematoxylin and eosin stain; $\times 7.5$.



Fig. 3 (case 1).—Proliferation of small vessels of the cord, and pronounced inflammatory round cell infiltration into the white and gray matter. A few pyknotic ganglion cells may be seen. Thionine stain; $\times 7.5$.

CASE 2.—History.—M. F., a white woman aged 70, was admitted to the hospital on Sept. 17, 1940, complaining of pain in her chest and her right shoulder. She dated her complaints to July, two months previous to admission, when she strained her shoulder in lifting

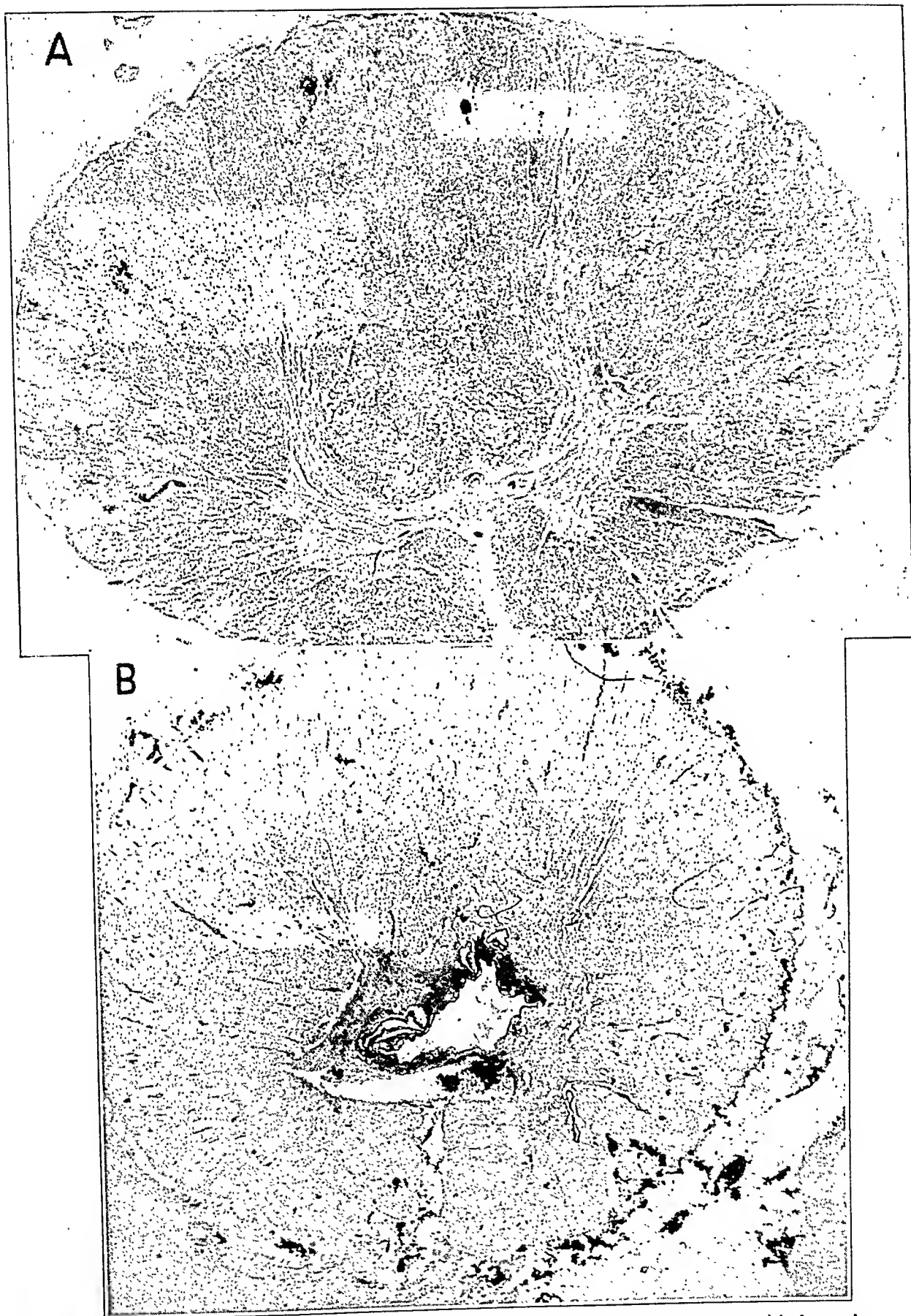


Fig. 4 (case 2).—*A*, patchy demyelination throughout the thoracic segments, with formation of lacunas. Weigert stain; $\times 10$. *B*, fibrous gliosis surrounding cavity in midthoracic region. Holzer stain; $\times 10$.

a weight. Since that time she had suffered pain in the right shoulder. In September, after another strain, she noted pain in her chest anteriorly and between the scapulas posteriorly. This pain was described as dull and constant and was aggravated during defecation and urination. Two days before admission she complained of weakness of both lower extremities, and this persisted. She could not empty her bladder except by pressing on her abdomen.

Examination.—On admission the temperature was 99 F., the pulse rate 80 and the respiratory rate 20; the blood pressure was 140 systolic and 80 diastolic. The pupils were pinpoint and reacted to light and in accommodation. The thyroid gland was uniformly enlarged and soft. The cranial nerves were normal. The lower extremities were weak bilaterally, but the reflexes were equal and active on the two sides. The abdominal reflexes were absent. The Babinski sign was not elicited. Position sense was diminished in the lower extremities, and vibratory sense was impaired as high as the iliac crests. There were hypesthesia and hypalgesia below the third rib anteriorly and the scapular spines posteriorly.

Course.—Weakness in the lower extremities was progressive, and reexamination on October 1 revealed the following changes: The pupils were small, the left being larger than the right, and both reacted sluggishly. There were nystagmus on lateral gaze and ptosis of the right lid. The lower extremities were completely paralyzed and flaccid. The knee and ankle jerks were absent; the abdominal reflexes were absent, and there was no response on

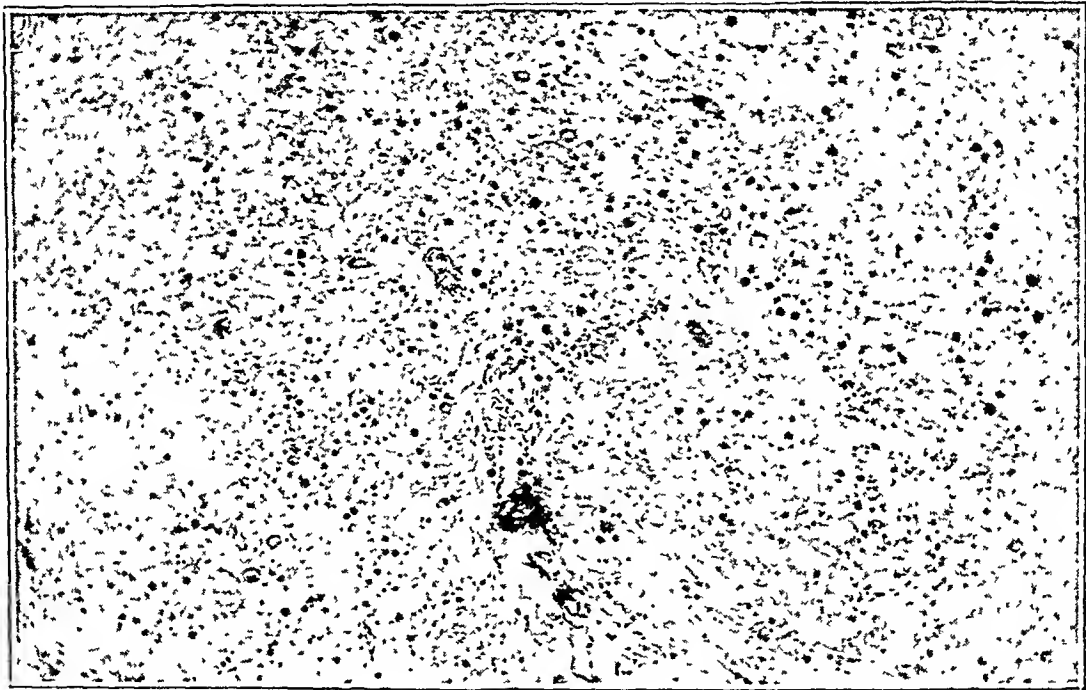


Fig. 5 (case 2).—Vacuolation or lacunar degeneration and frank necrosis; numerous corpora amylacea; hyperplasia of small vessels. Thionine stain; $\times 75$.

plantar stimulation. Marked relaxation of the sphincters was noted. Weakness extended to the upper extremities bilaterally, the right arm being affected more than the left. The deep reflexes here were equal and active on the two sides, and the Hoffmann sign was not elicited. Sensory loss corresponded to that noted previously. Lumbar puncture on October 1 revealed a clear, colorless fluid, with a pressure of 75 mm. of water. There was no rise on jugular pressure, and the rise and fall on abdominal compression were normal. The Pandy reaction was 4 plus, with a total protein content of 750 mg. per hundred cubic centimeters. There were 2 cells per cubic millimeter, of which 1 was a lymphocyte and the other a polymorphonuclear leukocyte. The Kahn reaction was negative; the colloidal gold curve was 5554444320. The Kahn reaction of the blood was negative. The basal metabolic rate was +3 per cent. The electrocardiogram was suggestive of myocardial fibrosis. A roentgenogram showed generalized demineralization of all vertebrae, with early spondylitis.

The patient complained of almost continuous pain in the shoulders and chest and of numbness and tingling in both arms and legs. She became progressively weaker and more helpless, and there was considerable muscular wasting. On October 8 coma ensued, with Cheyne-Stokes respiration, irregular, feeble pulse and a fall in blood pressure, and the patient died.

Necropsy.—There were carcinoma of the thyroid gland, with questionable metastases to the kidney; senile emphysema, and toxic changes in the spleen and liver.

The brain appeared entirely normal on gross examination. On palpation the upper thoracic portion of the spinal cord was moderately softened. Section at the fifth cervical level revealed a dusky gray discoloration in both anterior horns.

In the lower cervical and the upper thoracic segments, numerous areas of reddish discoloration were seen throughout the substance of the cord, particularly within the lateral and posterior gray horns and in the adjacent white matter. In the midthoracic region, the central canal appeared enlarged. From the sixth to the tenth thoracic segments, a large cavity was centrally located, being of maximal size at the eighth thoracic segment, where it measured 2 mm. in diameter. Below this region, and extending down to the first lumbar segment, the gray matter about the central canal appeared softened and mottled. The most caudal segments appeared normal on gross examination.

Microscopic preparations revealed extensive patchy demyelination throughout the upper thoracic region, imparting a diffuse moth-eaten appearance. Widespread fragmentation and formation of lacunas were noted where the myelin sheaths had been destroyed. The axicylinders were considerably swollen, and numerous compound granular corpuscles were seen. The neurons were pyknotic and shrunken and stained homogeneously. Chromatolysis and nuclear destruction were prominent. In the midthoracic region, the central portion of the cord was occupied by a large cavity. This extended from the region of the central canal into the adjacent gray matter. Pronounced gliosis, chiefly of the fibrous type, was seen surrounding this cavity.

The blood vessels, particularly in the areas which showed the most profound degeneration, were the seat of advanced changes. Hypertrophy of the intimal and the subintimal layer accompanied extreme narrowing of the lumen in the small vessels within the cord. Thrombosis and hemorrhage occurred in several of these vessels. The larger surface vessels, as well as the penetrating branches, showed moderate hyperplastic changes. No significant inflammatory infiltrations were seen.

The cerebral hemispheres and the brain stem presented no significant alterations.

CASE 3.—History.—J. M., a white man aged 36, was admitted to the hospital on April 20, 1942, complaining of weakness of the left leg and numbness and tingling of the right leg. About ten days previously he had noted cramplike pains in the right thigh. Two days later his left foot dragged and the leg felt heavy. Weakness was progressive, and a deep, dull pain persisted. Numbness of the right leg appeared a few days after the onset, and the extremity became tired easily and was somewhat weakened. The history was otherwise unrevealing.

Examination.—There was decided weakness of the left lower extremity, involving the thigh, leg and foot. The patient could lift the heel to the knee, but could not dorsiflex or plantar flex the foot, nor could he wiggle the toes. The deep reflexes were hyperactive in this extremity; ankle clonus was sustained, and there was a positive Babinski sign. Abdominal reflexes were absent bilaterally; the cremasteric reflex was present on the right side and absent on the left. All other reflexes were normal. There was no impairment for position, vibration or light touch sensation. There was analgesia for pinprick in the right lower extremity and over the trunk as high as the seventh rib on the right side, the area reaching just to the midline anteriorly and posteriorly. There was a greater degree of sweating on the left side than on the right. Nystagmus was noted on lateral gaze in either direction. Examination otherwise revealed nothing abnormal.

Lumbar puncture, performed the following day, revealed that the spinal fluid was clear and colorless, with normal pressure and manometric readings. There were 2 cells per cubic millimeter and 22 mg. of protein per hundred cubic centimeters. The Wassermann reaction was negative; the colloidal gold curve was 0000000000.

Course.—Two days after admission, the patient complained of pain in the left flank and difficulty in starting urination. Urinalysis and studies of the blood showed nothing significant, and a roentgenogram of the spine revealed no abnormalities. The patient left the hospital about a week after admission, with no essential change in his condition. He was again hospitalized on May 4. He had been catheterized regularly and had some fever, but the urine was not grossly infected. The paralysis had continued to ascend and now involved the left hand severely and the right hand to a lesser extent. The lower limbs were completely paralyzed and flaccid. Reflexes were diminished, and the Babinski sign was absent. The sensory level had ascended to the cervical dermatomes. There were complete loss of sensation below the nipple line, diminution of sensibility for all modalities as high as the eighth cervical segment and impairment of perception of pinprick up to the level of distribution of the trigeminal nerve. The patient was unable to turn over in bed or to breathe while lying

on his face. Priapism was noted, and there was nuchal rigidity with pain on forward flexion. No abnormalities of the cranial nerves were detected. Tympanites developed and became persistent.

Another spinal puncture revealed slightly xanthochromic fluid, with 320 cells, mostly leukocytes, and an increase in protein.

Large bed sores developed, and the patient died on May 21, about six weeks after the onset of symptoms.

Necropsy.—The brain showed no gross abnormalities aside from moderate edema. The spinal cord was removed intact, with the dura unopened. No abnormality was noted in the spinal canal. The dura was slit to expose the cord, the surface of which appeared grossly normal. Transverse section in the cervical region showed normal demarcation of the white and gray matter. The cord was edematous, and the cut surface rolled up. Section in the lower thoracic region disclosed a very soft, pulpy substance, and the gray matter could not be distinguished. The lower segments of the cord were softened. After fixation, sections revealed that the normal markings were obliterated below the midthoracic region.

Microscopic preparations revealed profound alterations within the spinal cord. In the lower thoracic and the lumbar and sacral segments scarcely any recognizable architecture could be made out. No nerve cells were preserved. In cross section, the cord was free from myelin and nerve fibers and presented a host of granule cells loaded with reddish-staining fat in sudan preparations, along with a delicate reticulum of connective tissue. Little gliosis, little



Fig. 6 (case 4).—Sections showing complete loss of form of the spinal cord, with hemorrhage into the parenchyma. Weigert stain; $\times 4$.

inflammatory infiltration and no inflammatory exudate over the meninges was evident. The process was intraspinal in extent. The central canal could usually be made out, but beyond this the tissue showed almost complete destruction. The vessels of the cord showed little change other than proliferation of new ones. The anterior spinal artery was intact in all sections.

The upper thoracic and cervical regions showed much better preservation, except in the myelin preparations, which revealed almost total loss of myelin in the dorsal columns, with large vacuoles in the ventral and ventrolateral regions. Fat-filled granule cells were fairly numerous, appearing chiefly in the dorsal columns. However, the ventral horn cells were also affected, showing rounded outlines, eccentric nuclei and loss of chromatin.

The process seemed to stop short of the medulla, and at the level of the nucleus of the twelfth nerve no myelin degeneration or reaction of any kind could be seen. No abnormality was observed in the pons, midbrain or cortex.

CASE 4.—History.—O. U., a white woman aged 55, entered the hospital complaining of paralysis of the legs and inability to void. Ten days prior to onset of the present illness she had had an acute infection of the respiratory tract, from which she recovered without apparent incident. On January 22 she noticed that the left hip was numb and then the left leg, and later in the day the left foot became paralyzed. On January 23 she was unable to urinate and the right leg became weak. She entered the hospital on January 25. The history was otherwise unrevealing.

TABLE 4.—Summary of Cases in Present Series

Age, Yr.; Sex	History and Onset of Illness	Clinical Observations	Course and Duration	Spinal Fluid	Postmortem Observations
42; female (Negro)	Sinusitis 3 yr. and hypertension 6 yr. Onset with obstipation, weakness of left leg, and then of left arm, with pain, followed by weakness of right leg; involuntary spasms	Weakness of all extremities atrophy; spasticity; hyperreflexia; pyramidal signs; increased threshold for position sense. Nystagmus; conduction deafness on right	After 2 wk. profound hypotonia below waist; sensory level to C 8; areflexia in lower extremities. Ascending urinary infection; decubitus; death 5 mo. after onset	(1) 20 lymphocytes; protein 175 mg. per 100 cc. (2) 3 cells; Pandy reaction +; protein 100 mg. per 100 cc.; Kahn reaction —; colloidal gold curve 433211100	Cervical portion of cord softened; structure disrupted on left side, white and gray matter destroyed. Vacuolation; mesodermal reaction; necrosis. Vascular hyperplasia. Lymphocytic infiltrations; compound granular corpuscles; nerve cell degeneration
70; female	Pain in chest and right shoulder following strain. Two mo. later, onset with weakness of lower extremities and difficult urination	Weakness of lower extremities; reflexes preserved. Sensory diminution below 3d rib; later, complete flaccid paralysis of lower extremities; areflexia; weakness of upper extremities. Nystagmus; ptosis	Pain in chest and shoulders; paresthesia of extremities; muscular wasting. Death 3 wk. after onset of weakness, 3 mo. after onset of pain	2 cells; Pandy reaction ++++; protein 750 mg. per 100 cc.; Kahn reaction —; colloidal gold curve 535444520. Pressure normal; manometric block	(Carcinoma simplex of thyroid; possible metastases to kidneys.) Spinal cord softened, maximal in thoracic region. Extensive demyelination; spongy appearance; compound granular cells; nerve cell degeneration. Syringomyelic cavity in thoracic region. Vascular hyperplasia; some thrombosis of small vessels. No inflammation
36; male	Weakness of left lower limb, numbness and tingling of right leg 10 days prior to examination	Weakness of left lower limb, with hyperactive reflexes, clonus and Babinski sign. Absence of abdominal reflexes and of cremasteric reflex on left. Impaired pain perception in right lower extremity and over trunk up to 7th rib level on right side	Ascent of paralysis to involve upper extremities; complete flaccid paralysis of lower limbs, with loss of reflexes; sensory level to cervical dermatomes for all modalities. Tympanites; priapism; nuchal rigidity. Urinary retention; loss of sphincter control; decubitus. Death 6 wk. after onset	(1) Clear, colorless; 2 cells; protein 22 mg. per 100 cc.; Wassermann reaction —. (2) Fluid xanthochromic; 330 cells (leukocytes); protein increased	Cord soft and pulpy from lower thoracic region down; normal markings obliterated; complete destruction of nerve cells, fibers and myelin. Numerous granule cells; little inflammation or gliosis. Proliferation of new vessels; others intact. Cervical segments better preserved; myelin and nerve cell degeneration. No involvement of brain stem or cortex
55; female	Infection of respiratory tract 10 days prior to abrupt onset. Numbness and weakness of left leg; urinary retention; weakness of right leg	Flaccid paralysis of lower extremities, with areflexia; sensory loss to Th 10 or 12	Ascent of paralysis to upper limbs; difficulty in deglutition and respiration; sensory level to clavicles. Death 2 wk. after onset	(1) Fluid yellow; 653 white cells, mostly polymorphonuclears; 439 red cells; protein 176 mg. per 100 cc.; Kahn reaction +; (blood Kahn reaction —); colloidal gold curve 112311000. (2) Deeply yellow; 32 red cells and 17 white cells (polymorphonuclears); Kahn reaction —; colloidal gold curve 444332900	Massive destruction of thoracic portion of cord, with herniation; no structures recognizable; necrosis, surrounded by zone of hemorrhage in lower thoracic region. Numerous glial cells; no inflammation. Vascular hyperplasia; fragmentation of elastica; thromboses

Examination.—The temperature ranged at about 100 F., the pulse rate about 100 and the respiratory rate about 20. The blood pressure was normal.

The cranial nerves were normal.

There was flaccid paralysis of the lower extremities, with loss of tendon reflexes. The lower abdominal reflexes were absent, and the upper ones were intact. Sensory examination revealed a complete loss of sensation extending to the level of the twelfth thoracic segment on the right side and to the tenth thoracic segment on the left side. Lumbar puncture on January 28 revealed hazy, pale yellowish fluid, under a pressure of 125 mm. of water. The total protein was 176 mg. per hundred cubic centimeters; there were 439 red blood cells and 658 white cells per cubic millimeter, with 95 per cent polymorphonuclears. The Kahn reaction was positive, and the colloidal gold curve was 1112311000.

The blood count was normal, and the Wassermann reaction of the blood was negative.

Roentgenograms of the spine and chest revealed nothing significant.

Course.—On February 1 the abdomen was distended and tympanitic. There was extension of the motor involvement to the upper extremities, with weakness of the hands and some difficulty in respiration. Analgesia now extended to the xiphoid cartilage and anesthesia to the umbilicus. All sensation was absent in the lower limbs, which were the seat of flaccid paralysis with areflexia. Lumbar puncture now revealed a deep yellow fluid, with 32 red blood cells and 17 white cells, 90 per cent of which were polymorphonuclears. The Kahn reaction was negative and the colloidal gold curve was 4444332200.

On February 2 there were slight cyanosis, difficulty in swallowing and inability to protrude the tongue. Ascent of the paralysis continued, and on February 4 an area of hyperesthesia, extending to the clavicles, was noted. There was no response to sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy, and death occurred on February 5, two weeks after the onset of symptoms referable to the spinal cord.

Necropsy.—Softening of the cord was extensive, with maximal involvement in the thoracic segments. In this region massive central necrosis was seen, with herniation of the substance of the cord through the incised dura. Microscopic preparations through these thoracic segments were so fragmented and distorted that the internal structures were difficult to recognize. A large central infarction with advanced coagulation necrosis, surrounded by a zone of hemorrhage, was seen in the lower thoracic segments. The higher thoracic segments showed somewhat better preserved architecture, but there was uniform cellular destruction, and only a few viable nerve cells remained in one portion of the anterior horn.

In the cervical region, sections revealed still better preservation of structure. Degenerative changes in the anterior horn cells were seen, and there was a pronounced vascular reaction. The latter was widespread throughout the cord and consisted of endothelial swelling of the small vessels, as well as moderate medial and intimal thickening of the larger ones. In many instances there was fragmentation of the elastica in the medium-sized vessels. About a number of the penetrating vessels of the cord there was a coagulated, acellular exudate, which stained deeply with eosin. Many of these vessels were thrombosed. Gitter cells were numerous throughout the areas of softening. No inflammatory reaction was seen, and a glial reaction could not be demonstrated.

Sections of the medulla and pons revealed no frank lesions. Cell stains showed a relatively normal picture, and myelin sheath stains here showed no remarkable degeneration.

COMMENT

A number of observations may be made from the foregoing descriptions. The cases recorded in the present report, as well as those summarized from the literature, fall under two heads: the acute and the subacute or chronic type.

The acute type varies in duration from ten days to three months. The onset is usually abrupt, with flaccid paralysis and complete sensory loss from the start. Pains and paresthesias are sometimes noted. Ascent of sensory and motor impairment may occur over a period of several days, although in a few instances the level remains stationary. An acute febrile course is occasionally seen, but for the most part fever appears with the advent of infection of the urinary tract or terminal infection of the respiratory tract. The spinal fluid in general shows an increase in protein and cells, although occasional dissociation and some normal fluids have been recorded. The course is progressive, without remission, and is invariably fatal. Anatomically, the striking feature is softening of the spinal cord, with

disruption of the normal structure. Destruction includes both the white and the gray matter as a rule, although some authors have described predominant involvement of the white matter. Both the myelin sheaths and the axis-cylinders are generally affected. In some areas a spongy or lacunar appearance is imparted as the result of diffuse demyelination. Cellular reaction is generally not of an inflammatory nature, although in some of the cases reviewed lymphocytic infiltrations were noted, and in a few polymorphonuclears were seen. Compound granular corpuscles are seen in large numbers. The intramedullary blood vessels are generally hyperplastic and sometimes thrombosed, and occasionally hemorrhages are noted.

The subacute or chronic type varies in duration from several months to two years or more. In an impressive number of cases weakness of the lower extremities is at first accompanied by increased tonus and hyperactive or well preserved reflexes, with subsequent change to flaccidity, atrophy and loss of reflexes. Sensory loss, as well as motor impairment, frequently shows ascent, and early sensory dissociation later becomes complete. The prevailing change in the spinal fluid is increase in protein, sometimes with pleocytosis, sometimes without. The pathologic changes include softening, usually maximal in the cervical or the thoracic region. Degeneration involves the white and the gray matter, although some authors have described predominant changes in the gray matter. Fragmentation, vacuolation or frank necrosis of the parenchyma, with homogeneous appearance and failure to stain, are seen. Demyelination, with a spongy appearance, may be noted. Vascular hypertrophy is frequent, the large extramedullary vessels being involved in some cases but the intramedullary vessels being affected more notably, with narrowing of the lumen. Necrosis or degenerative softening is generally most advanced in the neighborhood of the vessels which show most striking hyperplasia. Inflammation is characteristically absent, although not invariably. Occasionally lymphocytic infiltrations are described. Compound granular corpuscles are seen in many areas, and reactive glial changes may be present.

There is no intention here of classifying this general picture as an entity; rather, our purpose is to indicate trends and similarities in a number of diverse cases, some of which may represent the activity of a specific toxic or infectious agent.

It is interesting to note the general disagreement with regard to nomenclature. Among the early authors who criticized the inaccurate use of the term "myelitis" in referring to many different diseases of the spinal cord were Bastian,³⁸ Singer,³⁹ Biernacki,⁴⁰ Starr,⁴¹ Oppenheim⁴² and Henneberg.⁴³ These authors demonstrated that in many cases a condition designated as myelitis was actually softening due to vascular occlusion, and this view has long been substantiated.

Wilson coined the term "thrombomyelia" to describe the myelomalacias of varying origin. Numerous known precipitating factors have been described, the

38. Bastian, H. C.: Thrombotic Softening of the Spinal Cord as a Cause of So-Called "Acute Myelitis," *Lancet* 2:1531 (Nov. 26) 1910.

39. Singer, H. D.: Pathology of So-Called Acute Myelitis, *Brain* 25:332, 1902.

40. Biernacki, E.: Myelopathia endarteritica acuta, *Deutsche Ztschr. f. Nervenhe.* 10: 173, 1897.

41. Starr, M. A.: Organic Nervous Diseases, Philadelphia, Lea Bros. & Co., 1903, chap. 19.

42. Oppenheim, H.: Zum Kapitel der Myelitis, *Berl. klin. Wchnschr.* 28:761, 1891; *Lehrbuch der Nervenkrankheiten*, ed. 7, Berlin, S. Karger, 1923, p. 447.

43. Henneberg, R.: Die Myelitis und die myelitischen Strangerkrankungen, in Lewandowsky, M.: *Handbuch der Neurologie*, Berlin, Julius Springer, 1911, vol. 2, p. 694.

condition having been recorded as a sequel to influenza,⁴⁴ metastatic abscess,⁴⁵ Pott's disease,⁴⁶ antityphoid⁴⁷ and antirabic⁴⁸ inoculation, therapy with arsenical⁴⁹ and sulfonamide compounds,⁵⁰ toxic absorption from malignant tumors,⁵¹ indirect trauma,⁵² syphilitic³⁹ and arteriosclerotic⁵³ thrombosis, arteriosclerosis of the aorta, with occlusion of intercostal and lumbar arteries,⁵⁴ and embolism secondary to bacterial⁵⁴ or parasitic infection.⁵⁵

A contributing factor to the lack of uniformity in pathologic observations, and hence classification, may be that bacteria, as well as inflammatory cell infiltrations, can disappear early from true myelitic foci, with little remaining evidence of the inflammatory nature of the lesion. In the case of Cassirer and Lewy,^{45a} which was clearly one of metastatic myelitis, changes in the spinal cord were not unlike those noted in some of the cases reviewed in this paper, the lesions in the latter being usually ascribed to some toxic-infectious process or degenerative softening. The experimental work of Lotmar⁵⁶ presented further evidence of this fact. Injection of dysentery toxin into rabbits produced necrotic foci in the spinal cord, with degeneration of nerve elements and regressive glial changes, without much evidence of inflammation.

Variability of the inflammatory process is notable in cases of the disease following grip or influenza. Inflammatory changes were negligible in the cases of postinfluenzal myelitis included in our review, but were prominent in the cases described by Spiegel,^{44a} Puusepp^{44b} and others.

44. (a) Spiegel, O.: Myelitis nach Grippe, *Wien. klin. Wchnschr.* **32**:907, 1919. (b) Puusepp, L.: Akute aufsteigende Myelitis als Komplikation der Influenza, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **87**:377, 1923.

45. (a) Cassirer, R., and Lewy, F. H.: Ein Beitrag zur metastatischen Myelitis, *Monatschr. f. Psychiat. u. Neurol.* **52**:127, 1922. (b) Henneberg: Ascendierende, infiltrative Myelitis nach Erysipel, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **28**:240, 1922.

46. Hassin, G. B.: Histopathological Changes in Five Cases of Myelitis, *M. Rec.* **90**:619 (Oct. 17) 1916.

47. Divry; Moreau, M., and Ory: Myélomalacie à évolution foudroyante, survenue après une vaccination antityphique, *J. de neurol. et de psychiat.* **29**:369 (June) 1929.

48. Cacciapuoti, G. B.: Trombo-arterite midollare con sindrome di Brown-Séquard da vaccinazione antirabbica, *Cervello* **12**:189 (May) 1933.

49. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamines, *Am. J. M. Sc.* **189**:64 (Jan.) 1935. Mingazzini, G.: Klinischer und pathologisch-anatomischer Beitrag zum Studium der Myelitis haemorrhagica postsalvarsanica, *Deutsche Ztschr. f. Nervenhe.* **104**:1 (June) 1928.

50. Schubert, M.: Todesfall infolge Rückenmarkserweichung nach Uliron (Kombinations-schädigung), *Dermat. Wchnschr.* **107**:1361 (Nov. 19) 1938. Santo, E.: Ueber eine schwere Erkrankung des Rückenmarkes nach Ulironbehandlung einer Gonorrhoe, *Frankfurt. Ztschr. f. Path.* **53**:105, 1939. Germain, A., and Picard, P.: Myélite nécrotique subaiguë consécutive à l'injection intrarachidienne de 693 en solution sodique dans un cas de méningite cérébro-spinale, *Bull. et mém. Soc. méd. d. hôp. de Paris* **56**:670 (Nov. 25) 1940.

51. Spiller, W. G.: Rapidly Developing Paraplegia Associated with Carcinoma, *Arch. Neurol. & Psychiat.* **13**:471 (April) 1925.

52. Grinker and Guy.⁵⁸ Cadwalader.⁵⁹

53. Zeitlin, H., and Lichtenstein, B. W.: Occlusion of the Anterior Spinal Artery, *Arch. Neurol. & Psychiat.* **36**:96 (July) 1936.

54. Janota, O., and Jedlička, V.: Přisěvek ke kapitole o myelomalaciích, *Časop. lék. česk.* **74**:681 (June 21) 1935.

55. Rizzi, I.: Degenerative Myelitis Due to Echinococcus Embolism, *Riv. di pat. nerv.* **45**:397 (March) 1935. Dévé, F.; Lhermitte, J., and Trelles, J. O.: Myélomalacie, paralysie extenso-progressive secondaire à l'échinococcose intrarachidienne lombaire, *Rev. neurol.* **1**:623 (April) 1932.

56. Lotmar, F.: Beiträge zur Histologie der akuten Myelitis und Encephalitis, sowie verwandter Prozesse; auf Grund von Versuchen mit Dysenterietoxin, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena. G. Fischer, 1913, vol. 6, p. 248.

Some disagreement has recently arisen regarding the term "necrosis," which has been applied rather freely in the cases included in the present review. Hassin⁵⁷ differentiated softening and necrosis. He maintained that a necrotic area should be amorphous, devoid of blood vessels or any other tissue elements and incapable of staining. Other investigators have implied a more general process, characterized by destruction of the essential functioning elements of the tissue.

With regard to the etiologic factors and the pathogenesis, little can be added here which has not already been considered. In the cases reported the age incidence was predominantly between the third and the fifth decade, and the cases were almost equally distributed between the sexes. The history of a previous illness was in most cases questionably related to the onset of involvement of the spinal cord. In most instances no preceding illness was noted. In a few cases the presence of hypertension or albuminuria had been known. Lead colic had occurred in 1 of the cases of Foix and Alajouanine, and Moersch and Kernohan, in the investigation of their cases, made determinations of lead, with negative results. Gout was present in 1 case. In 3 cases the onset was associated with or shortly followed pregnancy and childbirth or abortion. In a relatively large number of cases (6) the disease occurred after infections of the respiratory tract, namely, grip or influenza. (Excluded from this study are the numerous cases of unquestioned postinfluenzal myelitis.) A known bacterial infection or local abscess preceded the onset of spinal symptoms in a small number of cases, and fever and chills without known infection, in an additional few. Direct trauma to the back, or indirect trauma by strain, preceded spinal symptoms by varying intervals in 5 of the cases included in this review. No evident vascular occlusion was noted in any of these cases. On the other hand, strain or indirect trauma caused softening and subsequent thrombosis in the cases of Grinker and Guy⁵⁸ and Spiller (cited by Cadwalader⁵⁹). It is possible that trauma may cause momentary vascular spasm or constriction, resulting in ischemic softening in one instance or actual thrombosis with softening in another.

Malignant tumor was discovered, or had preexisted, in some other organ in the cases of Nonne, Juba, Feindel, d'Antona and Moersch and Kernohan (case 3) and in our case 3. In Nonne's case there were metastases to the vertebral bodies, but the interspaces were intact and the meninges and cord free from metastases. The transmission of some toxic substance from the malignant tumor, by way of the blood stream to the spinal cord, has been suggested. There is no definite evidence for this assumption, but the possibility remains.

On the whole, the toxic and infectious factors seem more prominent than the degenerative elements in the cases reviewed. This has been the impression of many of the authors reporting these cases. It has frequently been remarked that parenchymal destruction has seemed most prominent in areas showing maximal vascular hyperplasia. Indeed, it has been the usual observation that little or no hypertrophy of blood vessels was seen outside these areas. One would expect a degenerative reaction to be more diffuse in the spinal cord, as well as in other viscera. On the other hand, a toxi-infectious agent reaching the spinal cord by hematogenous transmission might well cause a destructive process in the paren-

57. Hassin, G. B.: On Softening of Central Nerve Tissues, *J. Neuropath. & Exper. Neurol.* **1**:200 (April) 1942.

58. Grinker, R. R., and Guy, C. C.: Sprain of the Cervical Spine Causing Thrombosis of the Anterior Spinal Artery, *J. A. M. A.* **88**:1140 (April 9) 1927.

59. Cadwalader, W. B.: Observations on the Character of the Onset of Spinal Paralysis with Reference to the Significance of the Apoplectiform Type of Onset in Contrast to the Slow Progressive Development of Paralysis, *Arch. Neurol. & Psychiat.* **6**:541 (Nov.) 1921.

chyma and reactive hyperplasia of the blood vessels. It was the opinion stated by Foix and Alajouanine that such a process had in their cases affected the media of the vessels and the parenchyma of the cord simultaneously. In no subsequent case was there the extreme hypertrophy of the large extramedullary vessels, which were described by these authors as having an "onion skin" appearance. In case 2 of our series hypertrophy of these vessels was prominent (fig. 2), but not as remarkable as that noted by the French authors. Intramedullary vascular hyperplasia was seen rather consistently.

The occurrence of spasticity in the early phases in some cases, followed by flaccidity and loss of reflexes, is deserving of mention. It is likely that the early involvement of the white matter, with later destruction of the gray matter, accounts for this clinical feature.

SUMMARY

Necrosis or softening of the spinal cord has been described by numerous observers. Aside from the cases in which the cause was known to be thrombotic, traumatic, toxic or infectious, a general group may be considered in which the etiologic factors are obscure. These have been recorded under various headings, such as acute or subacute necrotic myelitis, progressive necrosis of the spinal cord, myelomalacia and myelodegeneration. There is little agreement regarding the etiologic factors or the nature of the pathologic changes.

The literature is reviewed, and 4 case studies are presented to indicate the general clinical pictures and the predominant pathologic changes.

It is suggested that in many of the cases reviewed, as well as in those presented, toxi-infectious causative factors and tissue reactions appear to exist. No specific agent has as yet been identified, but the possibility of its existence should be considered.

* Valley Forge General Hospital, Phoenixville, Pa.
1028 Connecticut Avenue.

INCLUSION BODIES AND LATE FATE OF GANGLION CELLS IN INFANTILE AMAUROTIC FAMILY IDIOCY

OTTO MARBURG, M.D.

NEW YORK

The changes in the ganglion cells in infantile amaurotic family idiocy are well known through the studies of Sachs,¹ Schaffer,² Bielschowsky³ and Spielmeyer,⁴ to mention only the leading investigators in this field. There are lacking, however, investigations concerned with the later fate of the altered ganglion cells in cases of infantile amaurotic family idiocy of long duration, as are studies of inclusion bodies, which are obviously related to the late changes in the ganglion cells. Finally it would be desirable to establish the relationship between the pathologic changes and the clinical signs, since these signs cannot be explained exclusively by the alterations in the ganglion cells, which are affected throughout the entire neuraxis.

For all these reasons the following cases were studied.

REPORT OF CASES

CHEMICAL STUDY

CASE 1.—L. S., a 3 year old boy, was admitted to the Jewish Hospital of Brooklyn, service of Dr. Leo Davidoff, on Dec. 12, 1941 and died on December 24.

Family History.—The maternal grandmother had a retroperitoneal sarcoma; the paternal grandfather, diabetes. There was no other familial disease in the family, which was traced back to the great-great-grandparents on each side. The patient had a brother with a condition diagnosed as Tay-Sachs disease in 1936 (Dr. Bernard Sachs); this brother was admitted to the Neurological Institute of New York on Feb. 13, 1935 and was dismissed on March 26 of the same year, with the diagnosis of amaurotic family idiocy. He died at the age of 15 months, of pneumonia.

Illness on Admission.—The patient appeared to be normal until the age of 3 months, when it was noted that he was irritable and was startled easily. Since this reminded the

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Dr. Leo Davidoff put at my disposal the history in case 1, and Dr. Max Lederer furnished the pathologic specimens.

This paper was begun in collaboration with Dr. Alexander Ellman, of the Brooklyn Jewish Hospital, who, however, had to discontinue the work because of service in the Army.

From the Department of Neurology, Columbia University College of Physicians and Surgeons; the Jewish Hospital of Brooklyn, and the Research Laboratory for Neuropathology, Montefiore Hospital.

1. Sachs, B.: (a) On Arrested Cerebral Development with Special Reference to Its Cortical Pathology, *J. Nerv. & Ment. Dis.* **14**:541, 1887; (b) On Amaurotic Family Idiocy: A Disease Chiefly of the Gray Matter of the Central Nervous System, *ibid.* **30**:1, 1903; (c) Pressing Problem Concerning Amaurotic Family Idiocy in Its Relation to Other Hereditary and Familial Diseases, in *Internationaler Neurologen-Kongress*, Copenhagen, Einar Nunksgaard, 1939.

2. Schaffer, K.: Ueber das morphologische Wesen und die Histopathologie der hereditär-systematischen Nervenkrankheiten, Berlin, Julius Springer, 1926; Die pathologischen Reaktionsformen des Neurons, *Hirnpath. Beitr.* **18**:37-42, 1938.

3. Bielschowsky, M.: Ueber spätinfantile familiäre amaurotische Idiotie mit Kleinhirnsymptomen, *Deutsche Ztschr. f. Nerven.* **50**:7-29, 1914.

4. Spielmeyer, W.: Klinische und anatomische Untersuchungen über eine besondere Form familiärer amaurotischer Idiotie, in Nissl, F., and Alzheimer, A.: *Histologie und Histopathologie. Arbeiten über die Grosshirnrinde*, Jena, Gustav Fischer, 1908, vol. 2, pp. 193-251.

mother of the sibling, the infant was given a thorough examination. Cherry red macular spots were noted in both eyes. The child was sent to the New York Hospital. After three weeks there amebic dysentery developed, from which he recovered in six months. In February 1940 he was again sent to the New York Hospital but was discharged in two weeks because of an infection of the upper respiratory tract. In September 1940 the child contracted pneumonia, from which he recovered in ten days. A few months after this it was noted that his head appeared to be larger than normal. Since then the head had increased steadily in size. During the three months before admission the patient lost consciousness three to four times a day for periods lasting up to one and a half minutes. During these periods the mother frequently saw the extremities shake. The patient was never able to sit up. He was able to move all his extremities, but the legs less than the arms.

Physical Examination.—The child was well nourished and did not look acutely ill. He appeared to be hydrocephalic. He was quiet and showed no interest in his surroundings. When he was startled there were tonic and clonic convulsions of the arms and legs. He maintained a position in which there were pronounced eversion of the hips, flexion of the knees and plantar flexion of the feet. He moved his arms spontaneously and the lower extremities only when disturbed. There was marked hypertonicity of all the extremities. The pupils did not react to light. The eyes did not follow a moving light. They blinked when a threatening move was made close to them. The head measured 58 cm. in circumference. The anterior fontanel admitted 1 finger and was shifted 2 cm. to the left of the midline. There was a corneal scar of the left eye. The disks were clear but atrophic. Cherry red macular spots were seen in both eyes.

Examination of the chest revealed Harrison's groove and coarse, bubbling bronchial rales.

Course in the Hospital.—The temperature rose to 104 F.; the respiratory rate increased to 56 a minute, and breathing became labored. Sulfadiazine (2-[paraaminobenzenesulfon-amido]-pyridine) was given by stomach tube, and the patient was placed in an oxygen tent. He died on December 24, at 11:15 p. m.

Laboratory Data.—The blood count, made on December 12, revealed 74 per cent hemoglobin, 4,900,000 red cells and 9,400 white cells, with 59 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes and 3 per cent monocytes. The number of platelets was adequate.

Urinalysis revealed acidity, a specific gravity of 1.008 and a faint trace of albumin.

Simultaneous lumbar and ventricular punctures, made on December 16, revealed no block. The colloidal gold curve showed no alteration. On December 17 the Kahn reaction, and on December 20 the Wassermann reaction, were negative.

Diagnosis.—The clinical diagnosis was Tay-Sachs disease, bronchopneumonia and hydrocephalus. The duration of the illness was two years and nine months.

The primary anatomic diagnosis was bilateral focal pneumonia, with *Staphylococcus aureus* and hemolytic streptococcus; bronchitis; macrocephalus with sclerosis (Tay-Sachs disease); thrombosis of the dural and cerebral veins; subarachnoid hemorrhage; fatty changes in the liver, and necrosis of the thymus gland.

Subsidiary changes were hydropic alterations in the adrenal glands and emphysema.

CASE 2.—An 18 month old Jewish girl was examined by Dr. Bernard Sachs, Dr. Louis Hausman and me (in private consultation). The family history was without significance except for a case of schizophrenia in the father's family; there was no consanguinity, and both parents were healthy. According to the parents, the disease began at the age of 9 months, but sight was disturbed some time earlier. There was general weakness; later blindness occurred. Ophthalmoscopic examination revealed optic nerve atrophy and cherry red macular spots. The child was lying in bed with the arms in slight flexion, the legs abducted and everted at the hips, the knees bent and the feet in the equinovarus position. There were hyperacusis and hyperpathia. The tendon reflexes were not exaggerated; there were no pathologic reflexes, but the abdominal reflexes were absent. No laboratory data were available except those from urinalysis, which were normal.

The child died of pneumonia at the age of 18 months.

The diagnosis was infantile amaurotic family idiocy. The duration of the disease was nine months.

CASE 3.—The case was one of Niemann-Pick disease with amaurotic family idiocy. The duration of the illness was nine months. This case was studied in collaboration with Dr. E. Epstein and was prepared for publication at the Neurological Institute of the University of Vienna in 1935.

CASE 4.—The case was one of amaurotic idiocy. The cortex has been described in a paper by Inaba.⁵

PATHOLOGIC STUDIES

CASE 1.—*Spinal Ganglia*.—In hematoxylin and eosin preparations the swollen cells showed a fine, dark blue dust around the nucleus, which was usually eccentric, while the cell body was bright red and contained very small granules. Occasionally the cell body appeared honey-combed, with vacuoles of varying sizes. In such a cell the cell body seemed to be represented by vacuoles of different sizes surrounded by plasma, since there were no red-staining granules. In some cells there were tigroid bodies around the nucleus; in others, neither tigroid bodies nor debris was evident. Occasionally the nucleus showed homogeneous shrinking. In some cells the debris was coagulated, while the nucleus formed a homogeneous, dark blue mass (fig. 1). Later the altered nucleus became coagulated with the homogeneous debris, whereas the rest of the cell body remained unchanged and took a reddish stain. In some cells this remnant of the cell body was also altered and stained pale blue, without presenting any structure. Finally, both these amorphous masses appeared coagulated. At this stage the cell was represented by a shrunken, amorphous mass, which stained blue with hematoxylin

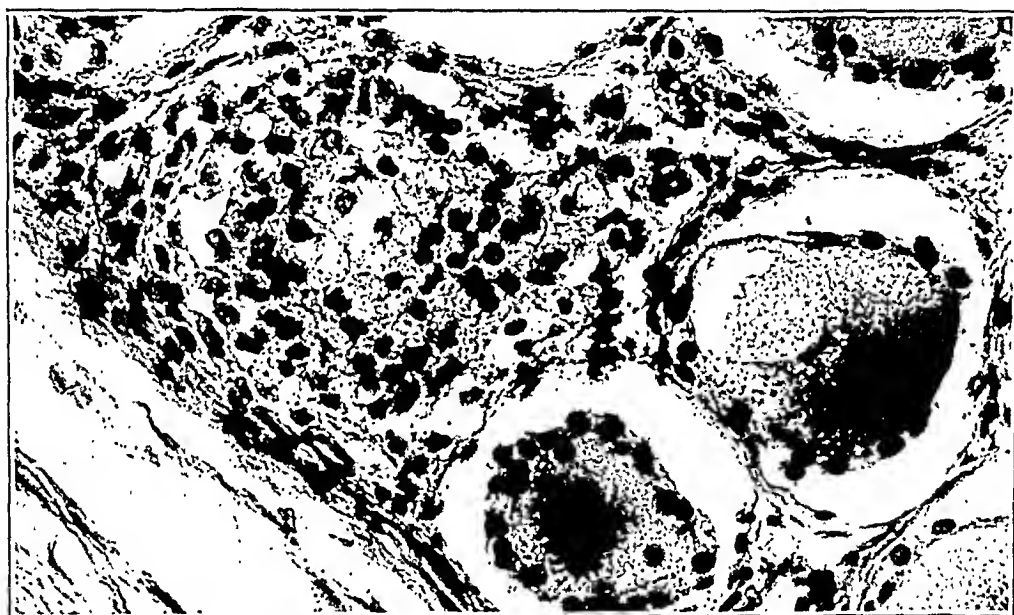


Fig. 1 (case 1).—Inclusion bodies from a spinal ganglion, showing one cell with vacuole and another resembling an amyloid body. Hematoxylin and eosin stain.

and resembled a cell only in shape. Some cells had completely disappeared, and the remaining gaps were filled with capsule cells.

Some of the spinal ganglion cells contained inclusion bodies (fig. 1). They were seen in a reddish ground substance, stained somewhat brighter red, as though some material was extracted, consisted of small globules and gave the impression that they were situated within a vacuole, apparently as a result of shrinkage. Some, however, were dark blue, like amyloid bodies (fig. 1, ventral cell). The picture was similar in Nissl preparations, in which the inclusion bodies stained pale blue.

With silver impregnation after the Bodian stain (fig. 2) two networks were stained: an interstitial one, in part regular, with very fine strands, and in part presenting thick and irregular strands; and a superficial network formed by fibrils which crossed each other and were intermingled with very fine sprouts of axons. The nucleus and the debris were black; the coagulated masses, grayish. The inclusion bodies were recognizable by a faint gray tint. The destruction of the ganglion cells caused an increase of capsule cells which filled the empty spaces.

5. Inaba, C.: Zur Frage der amaurotischen Idiotie, Arb. a. d. neurol. Inst. a. d. Wien. Univ. 30:360-366, 1928.

In sudan III preparations the cell bodies appeared light orange; they did not stain with osmic acid. In preparations stained with nile blue sulfate fine and coarse granules, as well as the inclusion bodies appeared darker blue than most of the finest granules.

The iron hematoxylin stain revealed a very fine black network in the inclusion bodies, with grayish granules within this network. Some granules in the cell bodies stained black.

Spinal Cord.—All the cells of the spinal cord were swollen (figs. 3, 4 and 5). Those of the posterior horn were less damaged than those of the anterior horn. In the smaller cells, such as those in Rolando's gelatinous substance, there was no debris, whereas the larger cells, particularly those in Clarke's column, presented the typical aspect of cells in infantile amaurotic family idiocy. Secondary changes were seen especially in the cells of the anterior horn. There were inclusion bodies (fig. 3), as well as transformation of the cell contents into amorphous masses (fig. 4). In addition to the amorphous masses formed within the cell,

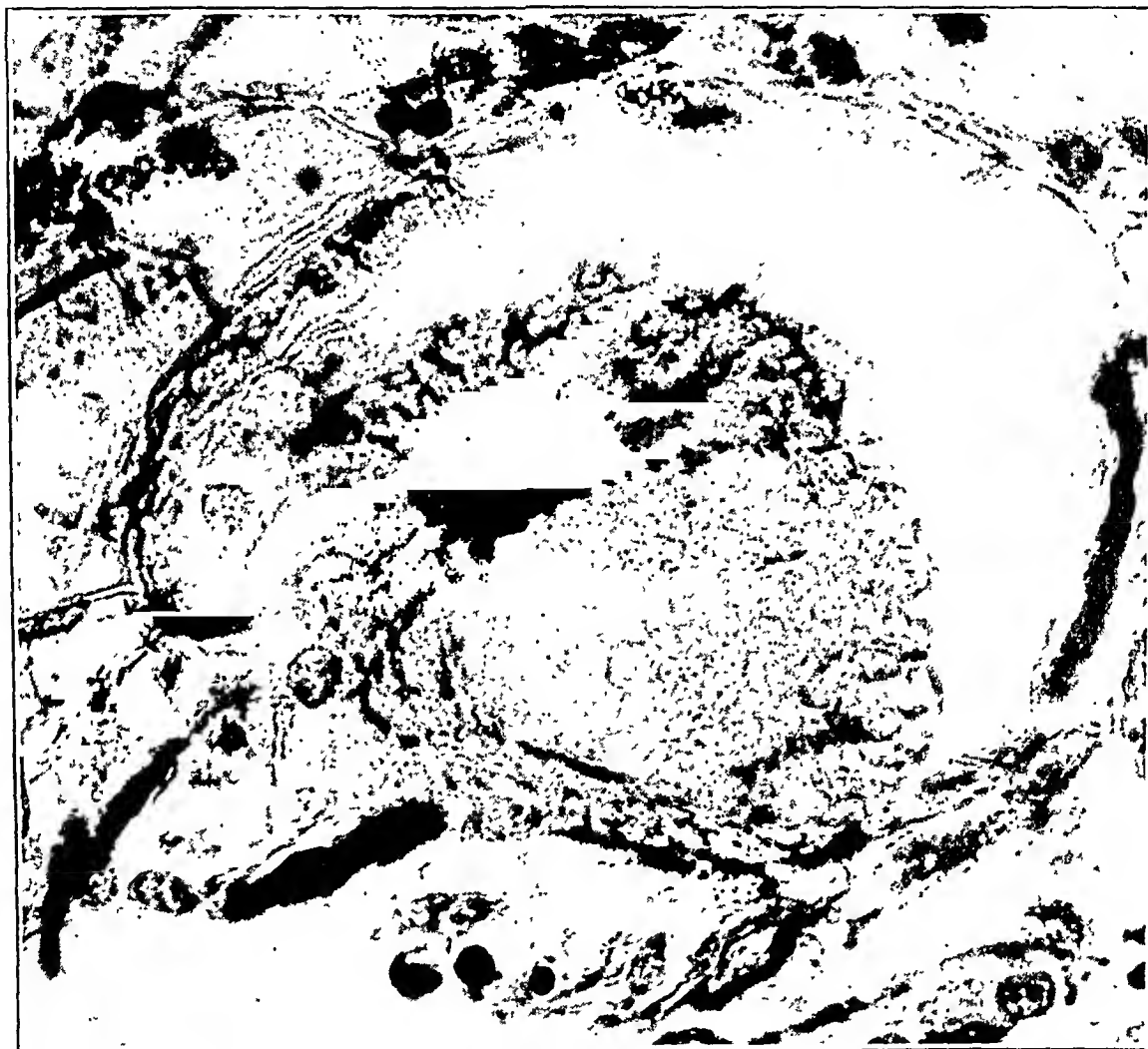


Fig. 2 (case 1).—Spinal ganglion, showing a superficial and an interstitial network; in the right upper corner of the cell is an argentophobic inclusion body. Bodian stain.

there were two other formations of such material. The first was easily recognizable by globular, sometimes irregular, masses arising from swollen axons (fig. 5); such formations are of frequent occurrence in cases of amaurotic idiocy. The second type of amorphous material lay apparently free in the tissue (fig. 6), without connection with ganglion cells or axons. All these amorphous masses stained the same color—pale blue with hematoxylin and grayish black with silver. In single cells there were sudanophilic granules (neutral fat[?]); in other cells single vacuoles or fat droplets of various sizes (fig. 4) were apparent.

Cerebellum.—Lack of ganglion cells was apparent in all layers. They were replaced by numerous scattered, round or pear-shaped bodies, the nature of which was easily revealed. Some of these globular bodies were remnants of swollen axons; others were compound granular cells, which stained black with silver, like the globules. A third type was seen in the molecular layer within dendrites of damaged Purkinje cells (fig. 7), obviously inclusion



Fig. 3 (case 1).—Inclusion body in an anterior horn cell. Hematoxylin and eosin stain.

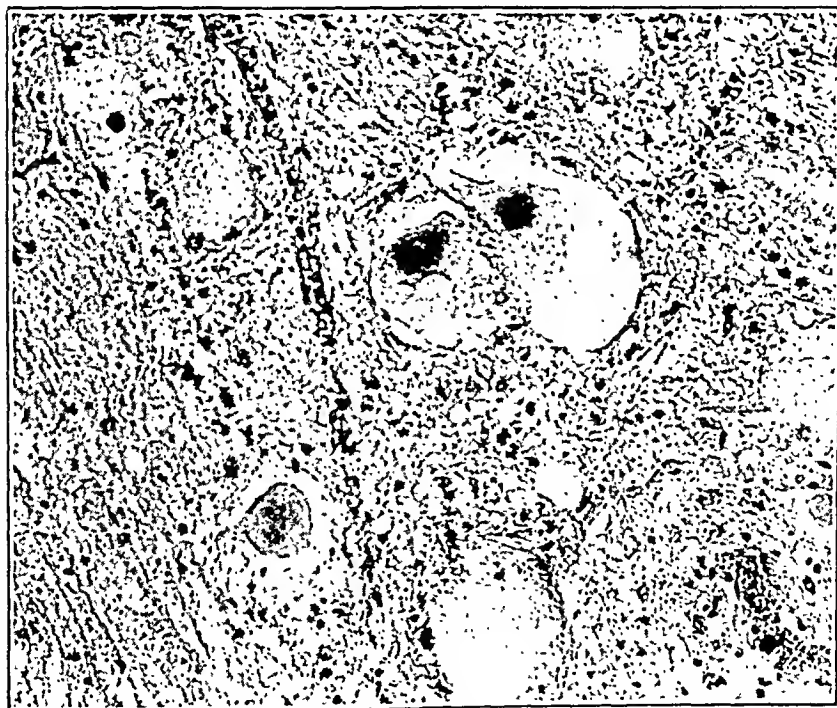


Fig. 4 (case 1).—Amorphous ganglion cell in the lower portion of the photograph; fat droplets of various sizes in the cell above it. Bodian stain.

bodies which had been partly liberated by the destruction of these cells. The dentate nucleus (fig. 8) was severely damaged. Inclusion bodies, as well as shrunken, homogeneous cells, were present, in addition to the well known lipoidosis. There was an increase in the glia, indicating destruction of cells. Axons were scanty, but a significant lack of myelin sheaths was not recognizable.

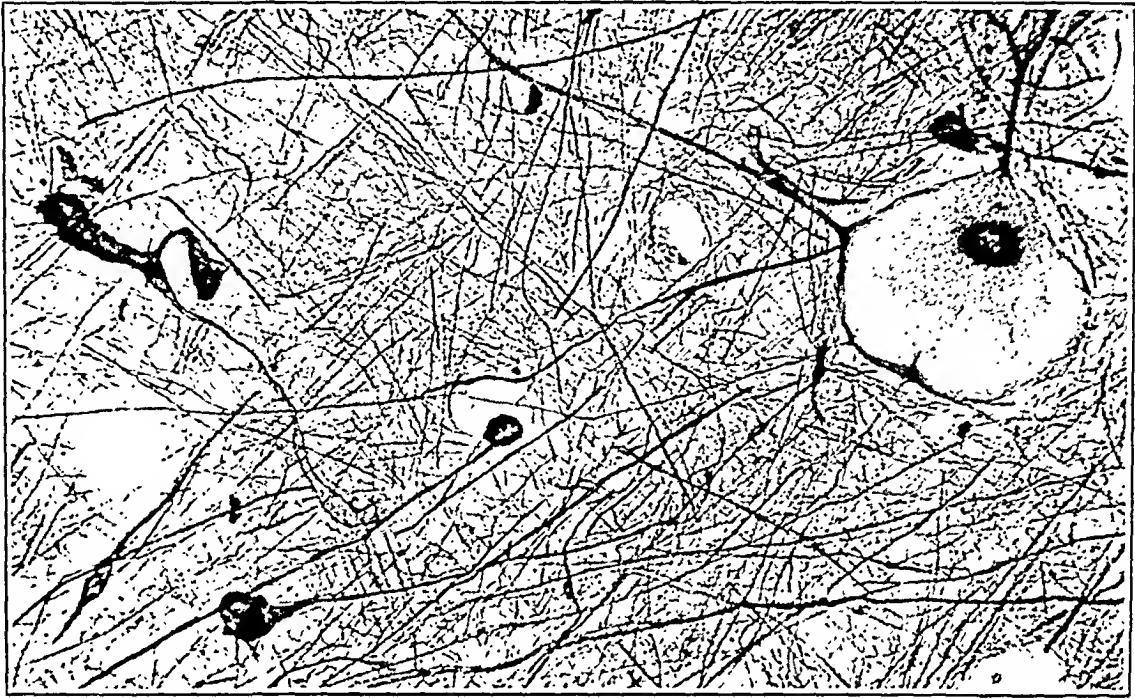


Fig. 5 (case 1).—Swollen cells from the anterior horn, with swollen axons. Bodian stain.

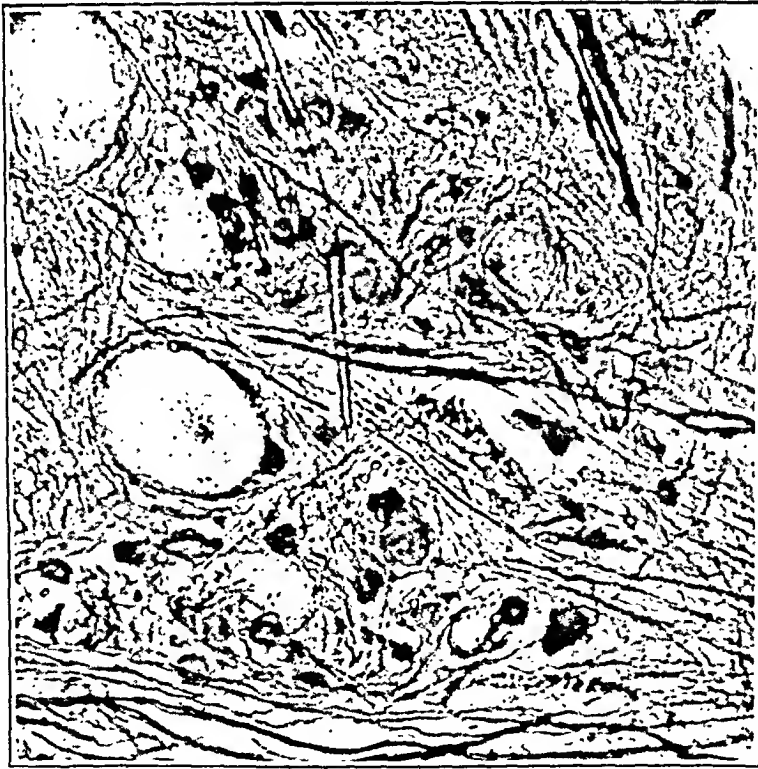


Fig. 6 (case 2).—Amorphous masses free in the tissues; swelling of axons. Bodian stain.

Cerebral Cortex.—All the cortical cells revealed a typical change. The Schaffer stain revealed that many of the ganglion cells were filled with lecithinophilic granules; others were scantily filled, and the ground substance stained reddish with picrofuchsin (fuchsinophilic). In sudan-stained sections the ground substance was bright orange.

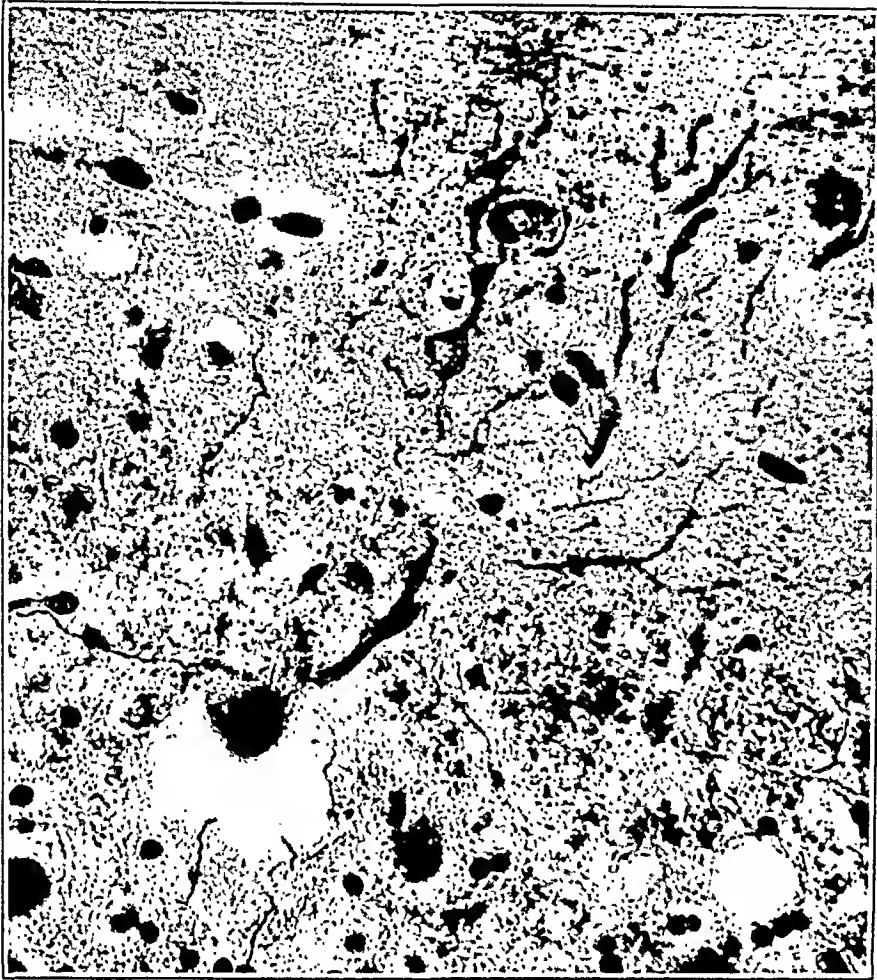


Fig. 7 (case 1).—Severely degenerated Purkinje cell, with three inclusion bodies in the dendrites. Bodian stain.

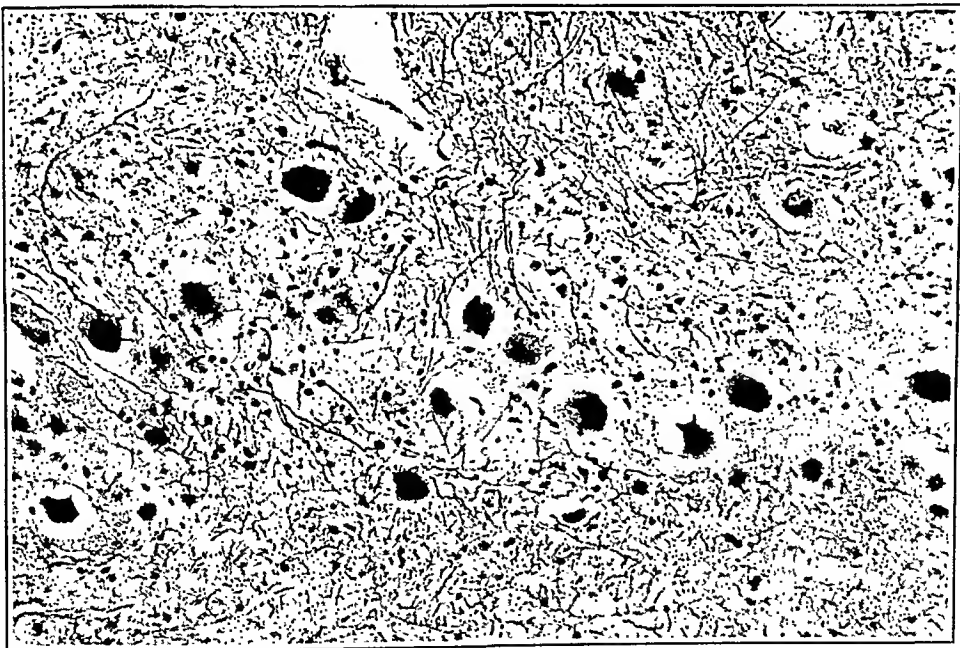


Fig. 8 (case 1).—Section from the dentate nucleus, showing precipitations (left) and destruction of cells (right). Bodian stain.

CASE 2.—While all the cells were degenerated, as in a typical case of infantile amaurotic family idiocy, most of the alterations in the cells described in case 1 were absent. There were only a few extracellular globules and irregular amorphous masses at the boundaries of the anterior horn (fig. 6). They originated partly from swollen axons, and some did not show any relation to surrounding structures.

CASE 3.—The cells in this case of Pick-Niemann disease were filled with hematoxylinophilic bodies; inclusion bodies were absent. In Bielschowsky preparations only the fibrils were impregnated; the cell contents remained unstained.

CASE 4.—All the cells were swollen, but no inclusion bodies or amorphous masses were observed.

COMMENT

The cell changes in cases of infantile amaurotic family idiocy obviously begin with swelling of the cell body, which may be of extreme degree. Closely associated with the cellular swelling are disintegration of the tigroid substance and the simultaneous appearance of fatty substances. The difference in these substances in the various forms of amaurotic family idiocy (infantile, late infantile, juvenile, adult and Pick-Niemann) is well known. The fat in infantile amaurotic family idiocy, as in Pick-Niemann disease, is hematoxylinophilic, but in the former it is not a phosphatide; in the late infantile form the hematoxylinophilic granules disappear, to be replaced to an increasing degree by sudanophilic and osmophilic granules. In cases of the longer-lasting infantile form as in case 1 in the present series, sudanophilic and osmophilic granules are seen, in addition to the hematoxylinophilic granules. Von Sántha⁶ claimed that in these longer-lasting forms the hematoxylinophilic granules, indicating the presence of prelipoids or phosphatides, disappear, and the occurrence of light orange-stained droplets then indicates the transformation of the granules into fat, approaching neutral fat. The same change is seen in case 1. In this case, there was in addition, a transformation of this fat partly or entirely to form inclusion bodies or amorphous masses, which led to the death of the cell.

The inclusion bodies in amaurotic family idiocy are of great interest. First described by Bielschowsky³ as black bodies with clear centers occurring in the dendrite of a Purkinje cell, they were later observed by other authors. One may agree with Bielschowsky that these inclusion bodies do not belong to the pathologic picture of amaurotic family idiocy. It is questionable whether the globules described by Schob⁷ correspond to these inclusion bodies. He observed them in the cells of the brain stem, where they stained bluish green with cresyl violet. Since in many cells there were fat droplets of different sizes and shapes, it is possible that Schob's granules were fat droplets. An accurate description of the inclusion bodies in cases of amaurotic family idiocy was given by Hassin.⁸ He noted them inside vacuoles in different regions (nucleus ruber; substantia nigra). But in the illustrations some of them are seen to be argentophilic (black); others do not stain with silver or show only a grayish tint. Since the consistency of the inclusion bodies is different from that of the surroundings, occasional shrinkage

6. von Sántha, K.: (a) Ueber drei reine, von Niemann-Pickscher Krankheit verschonte Fälle von amaurotischer Idiotie, *Arch. f. Psychiat.* **93**:675-766, 1931; (b) Neuer Beitrag zur Histopathologie der Tay-Sachs-Schafferschen Krankheit, *ibid.* **86**:665-676, 1929.

7. Schob, F.: Zur pathologischen Anatomie der juvenilen Form der amaurotischen Idiotie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **10**:303-324, 1912.

8. Hassin, G. B.: A Case of Amaurotic Family Idiocy: Late Infantile Type (Bielschowsky) with Clinical Picture of Decerebrate Rigidity, *Arch. Neurol. & Psychiat.* **16**:708-727 (Dec.) 1926.

may occur, as in case 1 in the present series, and the whole inclusion body may thus be removed, with a resulting empty vacuole on the slide. This is probably the explanation of some of the single vacuoles seen in sections in case 1.

Credit is due to Liebers⁹ for having been the first to attempt differentiation of the inclusion bodies by various staining methods. In his case amaurotic family idiocy was associated with myoclonus epilepsy, as in my case 1, but not to so pronounced a degree. The inclusion bodies, which were seen in the globus pallidus, the optic thalamus, the dentate nucleus and the nucleus ruber, resembled amyloid bodies; they were acidophilic, lecithinophilic or lipoidophilic, whereas stains for glycogen gave negative results. Somoza¹⁰ described inclusion bodies in Purkinje cells as second nuclei, whereas von Sántha,⁶ after thorough investigation, noted inclusion bodies throughout the nervous system in 3 cases of infantile amaurotic family idiocy. He described greatly enlarged cells containing only argentophilic bodies, with the nuclei pressed to the periphery. It is significant that he saw fibrils entering these bodies and that occasionally from the borders of the inclusion bodies silver-stained rays ran into the surrounding tissue.

In the present case there were inclusion bodies which reduced silver in Bielschowsky preparations, as well as inclusion bodies which did not reduce silver. Thus, there were two kinds of inclusion bodies: argentophilic and argentophobic. Both kinds stained almost equally well with other dyes. With hematoxylin and eosin or with fuchsin they stained red, or occasionally reddish blue; in Nissl preparations they were pale blue. The argentophobic bodies showed a slight affinity for hematoxylin, perhaps also for Nile blue sulfate, but they did not stain with osmic acid or scarlet red.

Most investigators have held these inclusion bodies to be amyloid bodies because of their similarity to amyloid bodies in the brain. Hassin⁸ claimed that they were colloidal substances, "though morphologically they, in some instances, much resembled amyloid bodies and chemically lipoids. Yet they were not affected by such chemicals as alcohol, xylene and ether."

It is impossible to discuss the origin of the inclusion bodies without considering the entire cell process in later stages. The two substances within the cell, namely, (1) the nucleus and the debris around it, chiefly protein, and (2) a fat mixture filling out the bulk of the cell, are changed in the later stages. The nucleus and the debris form a homogeneous mass which stains bluish black with hematoxylin, but the lipoids also become homogeneous, and their color changes from red to blue in hematoxylin and eosin preparations. Both of these substances then coagulate and form an amorphous mass, which stains grayish black in silver preparations and pale blue in hematoxylin and eosin sections. Occasionally one sees in a cell the nucleus only changed into a homogeneous mass, which stains black with silver. Thus, proteins, as well as lipoids, may finally stain black with silver.

In a recent paper I¹¹ described black granules in ganglion cells in cases of amaurotic family idiocy (silver reduction) and suggested that there is a process of dissolution in the cell in the course of which the tight linkage of protein and lipoids may be dissolved, with production of granules which stain black with silver.

9. Liebers, M.: Zur Histopathologie der amaurotischen Idiotie und Myoklonusepilepsie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **111**:465-484, 1927.

10. Somoza: Ueber eigenartige zweikernige Purkinjezellen bei der infantilen amaurotischen Idiotie, cited by von Sántha.⁶

11. Marburg, O.: Studies on the Pathology and Pathogenesis of Amaurotic Family Idiocy, *Am. J. Ment. Deficiency* **46**:312-322, 1942.

My later investigations¹² showed that the presence of protein is not necessary for the reaction because unsaturated fat also stains black with silver.

To study this problem more accurately, I¹³ proceeded as follows: An ammoniacal solution of silver, as used in Bielschowsky's method, was added to a small amount each of an unsaturated fat, a neutral fat and lecithin; no reaction occurred. The addition of calcium phosphate resulted in no reaction, and the only change on addition of a solution of ferric ammonium sulfate was a precipitation of reddish corpuscles. Then a drop of solution of formaldehyde U. S. P. was added to the three test fats in order to reduce the silver; the reduction occurred first in the unsaturated fat and later in the neutral fat, while lecithin inhibited prompt reduction. The result was the same on addition of calcium phosphate. The same experiment performed on a glass slide showed the entrance of silver into the unsaturated fat, whereas in the case of neutral fat silver accumulated around the droplets. Furthermore, a fat droplet to which calcium phosphate was added stained with hematoxylin; it showed a concentric arrangement of dye, the outer ring being dark bluish, the inner ring bluish red and the innermost part almost red. Iodine added to the three test fats did not change the color, but a mixture of iodine and calcium phosphate, which is brownish, kept its color when fat was added.

Since the similarity of the inclusion bodies to amyloid bodies has been emphasized by almost all neuropathologists, the question arises what role fat plays in the formation of the inclusion bodies.

Obersteiner¹⁴ described fat droplets in glia cells, which stained brownish black with osmic acid, the rest of the section remaining unstained. These droplets coagulate and then lose their affinity for osmic acid; they form homogeneous, sometimes concentrically arranged, bodies, which stain blue with hematoxylin. I saw them in hematoxylin and eosin preparations, being reddish in the early stages and later blue, while with the Bielschowsky method they stained black, like the inclusion bodies described by Hassin.⁸ Similar observations were mentioned by Casamajor.¹⁵ Thus, these bodies consist of fatty substances, so-called prelipoids, as suggested by von Sántha,⁶ or to a greater degree of unsaturated fat, as I¹² suggested.

Waelsch suggested that the nature of the fatty acids in lipoids may influence their properties so that they show the characteristics sometimes of a prelipoid and sometimes of unsaturated fat. Thus the nature of the fatty acids may change, together with the staining abilities of the respective cells.

In this connection one is reminded of the "brain sand" bodies (*corpora arenacea*, or psammous bodies). Investigations by Yoshimura,¹⁶ Windholz¹⁷ and me¹⁸ revealed the fact that the choroid plexus contains neutral fat intracellularly as well as extracellularly. Windholz¹⁷ assumed that this fat was the basis of the formation of the sand bodies, which stain first reddish with hematoxylin and eosin and later blue, the reaction obviously depending on the calcium content. It may be recalled

12. Marburg, O.: Studies in the Pathology and Pathogenesis of Multiple Sclerosis, with Special Reference to Phlebothrombosis and Guiraud's Bodies, *J. Neuropath. & Exper. Neurol.* **1**:3-13, 1942.

13. Marburg, footnotes 11 and 12.

14. Obersteiner, H.: Zur Histologie der Gliazellen in der Molecularschichte der Grosshirnrinde, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **7**:300-316, 1900.

15. Casamajor, L.: Zur Histochemie der Ganglienzellen der menschlichen Hirnrinde, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **18**:101-110, 1910.

16. Yoshimura, K.: Das histochemische Verhalten des menschlichen Plexus chorioideus, zugleich ein Beitrag zur Frage der Plexussektion, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **18**:1-12, 1910.

17. Windholz, F.: Konkrementstudien am Plexus chorioideus, *Verhandl. d. deutsch. path. Gesellsch.* **23**:296-301, 1926; Die Lipide des menschlichen Adergeflechts, *ibid.* **25**:353-357, 1930.

18. Marburg, O.: Hydrocephalus, New York, Oskar Piest, 1940.

here that Hofmeister¹⁹ suggested that in case of cleavage of fat the liberated fatty acids are effective as *Kalkfänger* ("calcium binders"). The concentric or the radial arrangement of the sand bodies is seen with fatty substances or mucin, as is well known in general pathologic studies.²⁰

Thus, one might well explain the presence of the inclusion bodies as the result of a process similar to that producing the brain sand and the amyloid bodies, developed on the basis of some kind of fat; their differences in silver-reducing ability may be due, as mentioned previously, to the presence of different fatty acids. The globules and amorphous masses free within the tissue still remain to be explained. In infantile amaurotic family idiocy these globules and irregular amorphous masses are formed by swollen axons, and they finally accept the same shape, size and color as the inclusion bodies within the cells. In this respect fat plays a role similar to that of inclusion bodies within the cells. This fat originates from broken myelin sheaths, and finally these extracellular, axon-developed bodies may approach the pattern of real inclusion bodies. Since in the cases reported by von Sántha⁶ fibrils entered into the inclusion bodies within the cells, the possibility cannot be excluded that some of the inclusion bodies take their origin from axons or fibrils, especially as one occasionally sees in cases of amaurotic idiocy a swelling of intracellular fibrils like that in Alzheimer's disease. Another explanation is that given by Alzheimer²¹ and Stürmer,²² that amyloid bodies are formed in free tissue fluid by precipitation. This possibility cannot be excluded in cases 1 and 2. These bodies lie within the boundaries of the gray matter. In addition to the glia cells and axons, fat lies partly free in the tissue or in histiocytes near blood vessels. Though it was impossible to determine the origin of all these inclusion bodies, some of them may well have been formed by precipitation in the tissue, as Stürmer²² suggested.

Thus, there are three possible ways of explaining the formation of inclusion bodies or amorphous masses in amaurotic family idiocy. The argentophobic inclusion bodies within the cells take their origin from a fatty substance, whereas it is not absolutely certain that this is true for the argentophilic bodies. It seems likely, however, with regard to the formation of amyloid bodies in glia cells. This circumscribed process can affect the whole cell, so that large amorphous masses are formed by the entrance of calcium, iron, glycogen or even protein. The kind of fatty mother substance and the amount of the entering material obviously influence the character of the inclusion bodies. These bodies indicate a change in cell metabolism—some kind of saponification, which is possible within ganglion cells as well as outside.

The significance of inclusion bodies in general is doubtful, for Lewy²³ observed them in association with parkinsonian states, as well as in the senium, and he

19. Hofmeister, F.: Experimentelles über Gewebsverkalkung, München. med. Wehnschr. 56:1977-1978, 1909.

20. Dr. Heinrich Waelsch, biochemist of the department of neurology, Columbia University College of Physicians and Surgeons, gave me the opportunity of discussing this subject with him.

21. Alzheimer, A.: Ueber die Abbauvorgänge im Nervensystem, Deutsche Ztschr. f. Nervenhe. 50:5, 1914; Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 3, pp. 401-562.

22. Stürmer, R.: Die "Corpora amylacea" des Zentralnervensystems, in Nissl, F., and Alzheimer, A.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913, vol. 5, pp. 417-518.

23. Lewy, F. H.: Ueber die Entstehung der Einschlusskörper und ihre Bedeutung für die systematische Einordnung der sogenannten Viruskrankheiten, Deutsche Ztschr. f. Nervenhe. 124:93, 1932; Die Lehre vom Tonus und der Bewegung, Berlin, Julius Springer, 1923.

therefore denied a relation between such bodies and infectious disease. I¹² suggested a differentiation of the inclusion bodies into three types: one arising from fat, the second caused by changes in axons and fibrils and the third formed by nuclear excretion. Only the third kind may be characteristic of infectious diseases, whereas inclusion bodies of the first and second types, associated with amaurotic idiocy, may be evidence of degenerative metabolic processes. But the latter two types, though characteristic of noninfectious disease, are also seen with infectious diseases. Thus, Godlowski²⁴ observed argentophobic inclusion bodies in cases of lethargic encephalitis and in Parkinson's disease, as did Lewy,²³ who, as previously mentioned, noted them in addition with senile and presenile states. The simultaneous presence of amyloid bodies in these conditions is well known (Adolf and Spiegel²⁵).

Some scientists identify the inclusion bodies in amaurotic family idiocy with those seen in myoclonic states. First described by Lafora,²⁶ and later by Lafora and Glück,²⁷ in cases of myoclonus epilepsy, these inclusion bodies resemble amyloid bodies and give similar staining reactions. Some of these bodies are argentophobic; some show a concentric arrangement and are also noted in glia cells (Davison and Keschner²⁸). Though these inclusion bodies are not specific, there is no doubt that they are seen in the great majority of cases of myoclonus, an indication of some relation to these states. In cases of amaurotic family idiocy in which inclusion bodies were present it is difficult to be sure whether such myoclonia existed, for the description of twitchings in these cases is inadequate and can hardly be evaluated. In Bielschowsky's³ case there was real epilepsy; in addition there occurred daily attacks of convulsions in the trunk and the muscles of the extremities, with fixation of the eyes, seizures which he called *petit mal*. In Hassin's⁸ case the parents told of "marked clonic contractions in the face, eyelids, and extremities," and examination revealed that the eyelids and the muscles of the lower extremities exhibited constant twitchings. In Liebers' ⁹ case there was real myoclonus epilepsy associated with amaurotic idiocy, whereas in the first case of von Sántha⁶ no twitchings were mentioned; in his second case there was tremor, which was relieved by phenobarbital, and in the third case there were convulsions resembling eclampsia and clonic convulsions in the distribution of the left seventh nerve and the upper extremities, occasionally lasting a few minutes. In case 1 in my series there were also myoclonic twitchings associated with epilepsy, resembling those in the case of Liebers.⁹

Thus it seems that in amaurotic family idiocy inclusion bodies are associated with convulsive states or myoclonia. In view of the fact that occasionally there are similar inclusion bodies in cases of Parkinson's disease and of postencephalitic parkinsonian states (Lewy,²³ Godlowski²⁴), it is understandable that they should be seen in a case of amaurotic family idiocy with tremor (second case of von Sántha⁶). Rarely, the inclusion bodies are absent in a case of myoclonia, or they are present without the occurrence of myoclonia (first case of von Sántha⁶). Thus,

24. Godlowski, W.: Die Ganglienzelleinschlüsse in der Substantia nigra, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **33**:14-23, 1931.

25. Adolf, M., and Spiegel, E. A.: Zur Pathologie der epidemischen Encephalitis, *Arb. a. d. neurol. Inst. a. d. Wien. Univ.* **23**:36-66, 1922.

26. Lafora, G. R.: Ueber das Vorkommen amyloider Körperchen im Innern der Ganglienzellen, zugleich ein Beitrag zum Studium der amyloiden Substanz im Nervensystem, *Virchows Arch. f. path. Anat.* **205**:295-303, 1911.

27. Lafora, G. R., and Glück, B.: Beitrag zur Histopathologie der myoklonischen Epilepsie, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **6**:1-14, 1911.

28. Davison, C., and Keschner, M.: Myoclonus Epilepsy, *Arch. Neurol. & Psychiat.* **43**: 524-545 (March) 1940.

one must admit that the inclusion bodies are of essential significance in myoclonic states. But they are not specific. They merely indicate that a particular kind of degeneration or metabolic cell change occurs more frequently with myoclonia than with other states. It may be emphasized that these other states are frequently associated with convulsions or hyperkinesia (epilepsy, Parkinson's disease, and perhaps postencephalitic parkinsonism). The time factor seems to play a role in the formation of the inclusion bodies in amaurotic family idiocy. Thus, in von Sántha's^{6b} youngest patient the disease lasted eighteen months; Hassin's⁸ patient suffered almost four years, Liebers' ⁹ patient was ill for three years, and the patient in case 1, two years and nine months, a period almost the same as that for von Sántha's^{6b} second patient (two and a half years). It is questionable, however, whether the time factor is the principal one. According to Liebers,⁹ two factors are operative in amaurotic family idiocy with myoclonia, one producing amaurotic idiocy and the other myoclonia. On the contrary, there is one common factor in the cases of amaurotic idiocy, namely, fat, which forms the content of the ganglion cells as well as that of the inclusion bodies.

In the papers on myoclonia associated with amaurotic family idiocy it is emphasized that the inclusion bodies are seen throughout the brain—for example, in Hassin's⁸ case, in the nucleus ruber and the substantia nigra. As previously mentioned, case 1 resembles the case of Liebers.⁹ The part most affected is the cerebellum, where the dentate nucleus is severely damaged and contains inclusion bodies. From his studies on the normal and the pathologic structure of the dentate nucleus in man, Tronconi²⁹ concluded that the described lesions of this nucleus are not specific, with one exception, namely, the inclusion bodies associated with myoclonus epilepsy.

Since all the parts of the brain which are held to be connected with hyperkinetic states are affected in cases of amaurotic family idiocy with myoclonia, it seems obvious that the site of the process, rather than the inclusion bodies, is responsible for the clonism. This opinion is in agreement with the view of Guillain and Mollaret,³⁰ who suggested a broader basis for the lesions leading to myoclonia (dentate nucleus—red nucleus—inferior olive). On the other hand, in a case of dyssynergia cerebellaris myoclonica (Ramsay Hunt³¹) the dentate system was affected, as in case 1.

There arises the question how the signs and symptoms in amaurotic family idiocy are produced. These signs are manifold. As a rule, one distinguishes a functioning and a vegetative part in the ganglion cells, a division which was first applied in cases of amaurotic family idiocy by Bielschowsky.³ Since the functioning part of the cells, the fibrils, remains intact for a long time, the influence of the severe changes in the cell plasma on the signs and symptoms may be comparatively small. In cases of longer-lasting disease the fibrils also are obviously damaged, followed by complete disintegration and disappearance of the ganglion cells. In such cases there are also lesions in the myelin sheaths associated with secondary degenerations and, of course, the corresponding clinical signs.

The clinical signs in the motor sphere are represented by general weakness and hypotonia. This weakness by no means resembles the paresis or paralysis in cases of degeneration of the anterior horn cells, for, according to Sachs,^{1a} the

29. Tronconi, V.: Osservazioni sulla fine struttura normale e patologica del nucleo dentato umano, *Riv. di pat. nerv.* **40**:137-240, 1932.

30. Guillain, G., and Mollaret, P.: *Études neurologiques*, Paris, Masson & Cie, 1936, series 7, pp. 3-83.

31. Hunt, R.: Dyssynergia Cerebellaris Myoclonica: Primary Atrophy of the Dentate System, *Brain* **44**:490, 1921.

reflexes are usually present and the electrical reactions of the muscles are normal except for occasional slight diminution of the response to the faradic current. I,¹¹ therefore, concluded from my recently published case "that every change in the vegetative part of a cell results in a change of the function of the nervous part," but that the asthenia in this case may have been caused in part by involvement of the adrenal system. Since the thymus was also severely damaged, this causative factor must also be taken into consideration. The atonic asthenia in amaurotic idiocy is quite different from the well known flaccid paralysis associated with degeneration of the anterior horn cells, and is therefore, if not entirely independent of the cell changes, dependent on them in part only. The cholinergic and the adrenergic factors are obviously damaged in a similar manner, as in myasthenia or in Addison's disease. In cases 1 and 2 the thymus and the adrenal glands were



Fig. 9 (case 1).—Degeneration of the pyramidal tract. Weigert stain.

altered, but these changes must be studied more accurately before they can be evaluated. It may be remarked parenthetically that Oppenheim's congenital myatonia obviously belongs also to this group of hypotonic asthenias. There are the same weakness and hypotonia, the same electrical reaction and the same position of the arms (handle position) and legs, followed by contractures, as are seen with amaurotic idiocy (Marburg³²).

In some cases of infantile familial amaurotic family idiocy signs of pyramidal disturbance occur, as in case 1, the result of degeneration of the pyramidal tract (fig. 9).

The most striking sign in amaurotic family idiocy is a negative one, the lack of sensory disturbances. As for the hyperpathia described in all cases of this disease, one must bear in mind that every blind person may be startled by a slight

32. Marburg, O.: Zur Klinik und Pathologie der Myatonia congenita (Oppenheim), Arb. a. d. neurol. Inst. a. d. Wien. Univ. 19:133-154, 1912.

touch or a sudden noise. In any case, it is surprising that such severe damage of all sensory cells (spinal ganglion; posterior horn) has no other consequence than hyperirritability.

The optic nerve is affected in such a manner as to produce blindness. The white papilla indicates demyelination of the optic nerve, caused by the changes in the retina cells and their disappearance. The disappearance of many ganglion cells and the severe impairment of the outer fiber layers of the cerebral cortex doubtless cause the idiocy, but the characteristic change in the cortical cells does not result in any other signs. As long as fibrils remain intact and there are no secondary degenerations, the vegetative changes in the ganglion cells are obviously not followed by clinical signs seen with lesions involving degeneration of the functioning part.

With respect to these facts there is no difference in the various forms of amaurotic family idiocy. Most authors, however, emphasize differences between Pick-Niemann disease and other forms of the disease, though the former condition resembles infantile amaurotic family idiocy in many respects. These differences concern the kind of fat within the cells, the occurrence of secondary changes in the affected ganglion cells and the site of the process (in amaurotic family idiocy, the nervous system principally and in Pick-Niemann disease, the whole body). Infantile amaurotic family idiocy and Pick-Niemann disease are identical with regard to affinity of the fat for hematoxylin, whereas the constitution of the fat is different (Klenk³³). The fat in Pick-Niemann disease is sphingomyelin; that in infantile amaurotic family idiocy contains a fatty substance resembling the cerebrosides (Klenk³³). This fat in the infantile type presents some of the characteristics of phosphatides—hematoxylinophilia, for instance. In cases of the late infantile form this fat is substituted in great degree by sudanophilic or osmophilic granules, commonly regarded as neutral fat, which is otherwise seen only in cases of the juvenile and adult types. Von Sántha⁶ noted diminution of hematoxylinophilic granules in his cases; these granules stained light orange with scarlet red. In the present case 1 there was also diminution of hematoxylinophilic granules, and in some cells there were very fine granules of a sudanophilic or osmophilic nature. It seems that in cases of longer duration—the shortest period in von Sántha's cases was eighteen months, and in his third case the duration was two and a half years, almost like that in case 1—there is a final transformation of lipoids into a fat that stains with osmic acid and with scarlet red (neutral fat[?]). Thus, the difference in the lipoids in infantile and in later forms of amaurotic family idiocy may be due merely to the duration of the process.

As for the site of the process, it may be emphasized that the intensity of the damage varies in different regions in different cases. Sometimes the cerebellum and sometimes the striopallidum are severely altered, with production of the corresponding local signs. The cause of this rather individualistic reaction has not yet been revealed. But it certainly is a severe lesion, a lack of functioning tissue, which produces the local signs.

Thus Bielschowsky's³ suggestion that some peculiarities seen in cases of juvenile amaurotic family idiocy are not present in cases of the infantile type, the degenerations for instance, appears untenable. All changes observed in cases of juvenile amaurotic family idiocy are also seen in those of infantile amaurotic family idiocy if the duration is only long enough.

33. Klenk, E.: Beiträge zur Chemie der Lipoidosen, *Ztschr. f. physiol. Chem.* **262**:128, 1939.

SUMMARY

Investigation of several cases of infantile amaurotic family idiocy has revealed the existence of inclusion bodies and severe secondary cell degeneration.

The inclusion bodies are partly argentophilic and partly argentophobic, depending on the kind of fat which forms their basis.

In cases in which inclusion bodies are present there are almost always myoclonic states.

Precipitations outside the cells are caused by degeneration of axons. It cannot be definitely decided whether there are also precipitations from the tissue fluid (Alzheimer and Stürmer).

The clinical signs in cases of infantile amaurotic family idiocy are due only in part to the well known cell changes, which affect merely the vegetative, and not the functioning, portion (fibrils). Only when the functioning part also is affected do neurologic signs appear.

The atonic asthenia, like that in myasthenia or in Addison's disease, is to be explained by a disturbance in cholinergic and adrenergic factors, obviously the result of changes in the thymus and the adrenals which are observed with infantile amaurotic family idiocy.

630 West One Hundred and Sixty-Eighth Street.

FATAL CEREBROVASCULAR ACCIDENT ASSOCIATED WITH CATATONIC SCHIZOPHRENIA

REPORT OF A CASE

J. P. MURPHY, M.D.

AND

META A. NEUMANN, M.S.

WASHINGTON, D. C.

A classic description of acute fatal catatonia was given by Calmeil¹ in 1832. The prominent features observed by him were vivid hallucinations, vasomotor instability and fluctuation from wild hyperactive states to profound stupor. There was rapid progression of the illness to death. He added: "The autopsy explains nothing."

After a lapse of one hundred and ten years this statement still holds good. The neuropathologist has found little in studies of fatal catatonia that can be considered as the specific anatomic substrate of the syndrome. Reichardt,² Josephy,³ Scheidegger,⁴ Stauder⁵ and Jahn and Greving⁶ report the presence of "brain swelling" in some of their cases of sudden death during an episode of acute catatonia, but this is by no means a consistent observation.

From the microscopic standpoint, many detailed accounts of neuropathologic changes have appeared. Goldstein⁷ reported changes in the ganglion cells, focal necrobiotic lesions and glial activity in the cerebral cortex. Josephy³ made essentially the same observations, emphasizing their diffuse character. Vascular stasis and perivascular hemorrhages were noted by Claude and Cuel⁸ and also by von Braunnmühl.⁹ Spielmeyer¹⁰ noted similar lesions but called them nonspecific. He pointed out that he found just such changes in the brains of normal persons, as well as of persons with pathologic conditions not primarily associated with dementia.

The most recent addition to the literature of acute schizophrenic catatonia is the case reported by Malamud and Boyd.¹¹ Their patient was a 20 year old woman

From St. Elizabeths Hospital, Washington, D. C.

1. Calmeil, cited by Ladame, C.: *Psychose aiguë idiopathique ou foudroyante*, Schweiz. Arch. f. Neurol. u. Psychiat. **5**:3, 1919.

2. Reichardt, M.: *Hirnschwellung*, Allg. Ztschr. f. Psychiat. **75**:34, 1919.

3. Josephy, H.: *Beiträge zur Histopathologie der Dementia praecox*, Ztschr. f. d. ges. Neurol. u. Psychiat. **86**:391, 1923.

4. Scheidegger, W.: *Katatone Todesfälle in der psychiatrischen Klinik von Zürich von 1900 bis 1928*, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:587, 1929.

5. Stauder, K. H.: *Die tödliche Katatonie*, Arch. f. Psychiat. **102**:614, 1934.

6. Jahn, D., and Greving, H.: *Untersuchungen über die körperlichen Störungen bei katatonen Stuporen und der tödlichen Katatonie*, Arch. f. Psychiat. **105**:105, 1936.

7. Goldstein, K.: *Zur pathologischen Anatomie der Dementia praecox, im besonderen der plötzlichen Todesfälle bei derselben*, Monatschr. f. Psychiat. u. Neurol. **25**:565, 1909.

8. Claude, H., and Cuel, J.: *Notes anatomo-cliniques sur trois cas de délire aigu*, Encéphale **22**:628, 1927.

9. von Braunnmühl, A. V.: *Ueber Gehirnbefunde bei schweren Erregungszuständen*, Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:163, 1928.

10. Spielmeyer, W.: *Kreislaufstörungen und Psychosen*, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:536, 1930.

11. Malamud, N., and Boyd, D., Jr.: *Sudden "Brain Death" in Schizophrenia with Extensive Lesions in the Cerebral Cortex*, Arch. Neurol. & Psychiat. **41**:352 (Feb.) 1939.

who showed hypotension, acrocyanosis and menstrual irregularities during nine months of hospitalization. During a period of catatonic excitement she lapsed into coma. There followed a series of generalized convulsions, signs of meningeal irritation and hyperpyrexia. Death occurred sixty-eight and a half hours after the onset of the acute episode. Anatomic studies revealed multiple, discrete and coalescing areas of hemorrhagic encephalomalacia throughout the cortex of the cerebrum and the cerebellum. Many of these areas were rather large. There were no evidences of a major vascular accident; in fact, no changes were demonstrated in the blood vessels. The authors attributed the lesions to a functional disturbance of the cerebral circulation associated with constitutional vasomotor lability, and not directly to the psychosis.

REPORT OF CASE

History.—S. L. J., a 22 year old white man, was admitted to St. Elizabeths Hospital on May 2, 1942.

One brother was said to have suffered from a "nervous breakdown." The patient ran away from home because of discontent with the family situation. Shortly afterward he enlisted as a yeoman in the United States Coast Guard. He had two years and seven months of active duty, with a good conduct rating, before the present illness.

On April 29, 1942 the patient wedged himself in the bilges of a coast guard cutter; the reason he gave for this act was: "I'm a coward." He was admitted to the United States Marine Hospital, Norfolk, Va., on the following day. While there he was disturbed and negativistic, appeared to be deeply concerned about loyalty to his mother and to his country, manifested delusions of unworthiness and declared that he believed he had syphilis. Insight was lacking, and judgment was faulty. Asked to undress, he at first refused to do so, but later tore off his clothing. He escaped from a locked room by destroying a heavy screen, ran down a fire escape in the nude and attempted to start a truck and leave the hospital grounds. It was necessary to employ several orderlies to subdue him. He was then transferred to the United States Naval Hospital, Bethesda, Md., and from there to St. Elizabeths Hospital.

He arrived on a stretcher, in restraint. He was mute except when in a cold pack. At such times he talked freely, but often incoherently. His emotional reactions were inappropriate. Lability of mood was striking. He admitted having auditory hallucinations and expressed many delusions. Attention wandered, and comprehension was faulty. He was disoriented for place.

Physical Examination.—Examination disclosed a well built young man with dusky red-mottled skin. The blood pressure was 128 systolic and 96 diastolic and the pulse rate 90 beats per minute. The pupils were round and equal. They reacted briskly to light and in accommodation. The optic disks were flat. No retinal vascular abnormalities were observed. The deep reflexes were equal and active on the two sides. The only abdominal reflex obtained was in the right lower quadrant. The whole body surface was practically immune to superficial pain. Perception of pressure pain was diminished.

The diagnostic impression was dementia praecox (schizophrenia), catatonic type, with affective features.

Course of Illness.—He was violent and profane and needed restraint except when under the influence of sedative drugs. Cold packs were also useful in calming him. He refused to eat; it was necessary, therefore, to resort to tube feeding on the third day in the hospital. This could be accomplished only after the intravenous administration of sodium amytal ($3\frac{3}{4}$ grains [0.24 Gm.]). After the feeding he manifested no weakness of the arms or legs. He displayed many infantile mannerisms.

Sometimes during the night he lost the use of the right arm and leg. He was found lying on the floor, unable to move these extremities. Neurologic examination now revealed weakness of the right side of the face; right flaccid hemiplegia; absence of deep reflexes in the right arm; absence of abdominal reflexes on the same side, and a positive Mayer's sign. The blood pressure was 130 systolic and 80 diastolic, the pulse rate 92 and the temperature 100 F. (rectal). Lumbar puncture made shortly afterward demonstrated an initial spinal fluid pressure of 140 mm. of water. The specimen was clear and colorless. There were 4 cells per cubic millimeter; the protein content was not increased. The Kolmer and colloidal gold reactions were negative.

Eight hours later the patient was in deep stupor. The blood pressure had fallen to 75 systolic and 52 diastolic. The temperature remained elevated. The neck was not stiff. Breathing was slow and deep, and there was a noticeable lag of the right side of the thorax. During periods when he partially awakened he appeared to be completely aphasic. Confrontation examination of the visual fields at these times demonstrated probable right homonymous hemianopia. Occasionally there was skew deviation of the eyes. The pupils were round, equal and moderately dilated. The optic disks were not edematous. No vascular or retinal changes were noted. Sucking and biting reflexes were elicited with ease. There was weakness of the right side of the face of supranuclear type. The right arm and leg were flaccid and immobile. A grasp reflex was present in the right hand. The deep reflexes were active and equal in the two arms but were accentuated in the right leg. Cutaneous reflexes could not be obtained. The Hoffmann response was demonstrable in

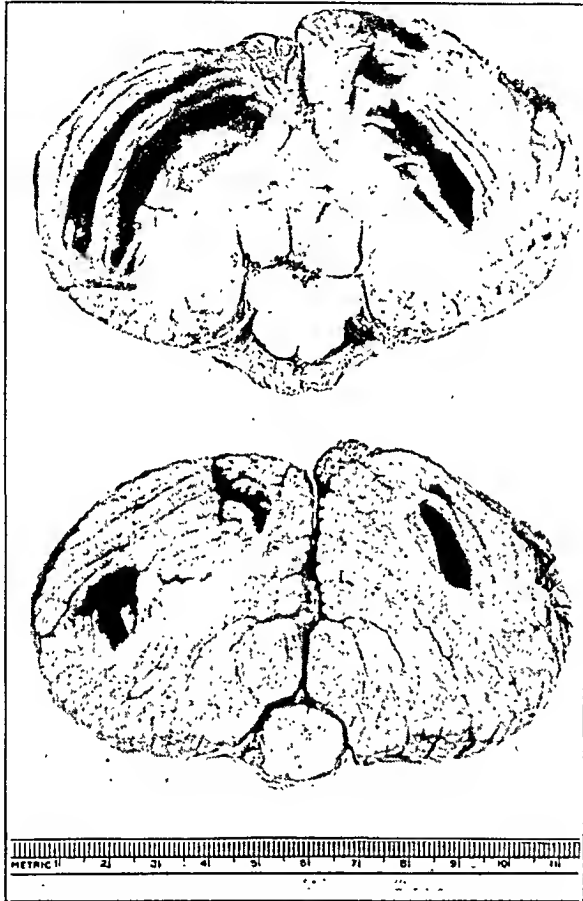


Fig. 1.—Subarachnoid and parenchymal hemorrhages in the cerebellum.

both hands, but the plantar reaction was flexor in type. Sustained ankle clonus was elicited bilaterally. Appreciation of pinprick was reduced over the whole right half of the body.

The patient was given 500 cc. of blood plasma and, later, 1,000 cc. of 10 per cent dextrose in saline solution. One hundred milligrams of nikethamide, 50 mg. of thiamine hydrochloride and 100 mg. of ascorbic acid were administered intravenously. By this time his general condition was somewhat improved, and the blood pressure had risen to 120 systolic and 70 diastolic. Aspiration of much mucopurulent material from the tracheobronchial tree resulted in the disappearance of coarse rales from the lower lobes of the lungs.

He lived five days longer, his condition fluctuating between stupor and wakefulness. During the intervals of wakefulness he became active and combative and had to be restrained. The neurologic status remained essentially unchanged. Many examinations of the eyegrounds failed to disclose choking of the disks. A blood count revealed moderate leukocytosis but no increase in the number of erythrocytes. The bleeding and clotting times were normal. A second spinal tap, on the sixth day in the hospital, yielded no fluid. Repeated aspiration of the chest and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) medication resulted

in a temporary fall of body temperature to a nearly normal level. On the ninth hospital day the temperature again rose, however, to 104 F. (rectal); the respirations became slow and labored; generalized cyanosis appeared, and the patient died.

Necropsy.—Postmortem examination was performed eighteen hours after death by Dr. K. H. Langenstrass. The body was that of a well developed and well nourished young man. There were a number of small abrasions in the gluteal region. The subcutaneous fat and the pectoral and abdominal muscles were rather dry. The heart was dilated, poorly contracted and soft. There were no valvular or myocardial lesions. The aorta and the large vessels were thin walled and elastic. The aorta measured only 40 mm. in diameter at the level of the celiac axis. The lungs showed marked hypostatic congestion and edema. There was purulent bronchitis. The abdominal viscera showed no evidence of a disease process, except for pronounced hyperemia. The endocrine system appeared grossly normal.

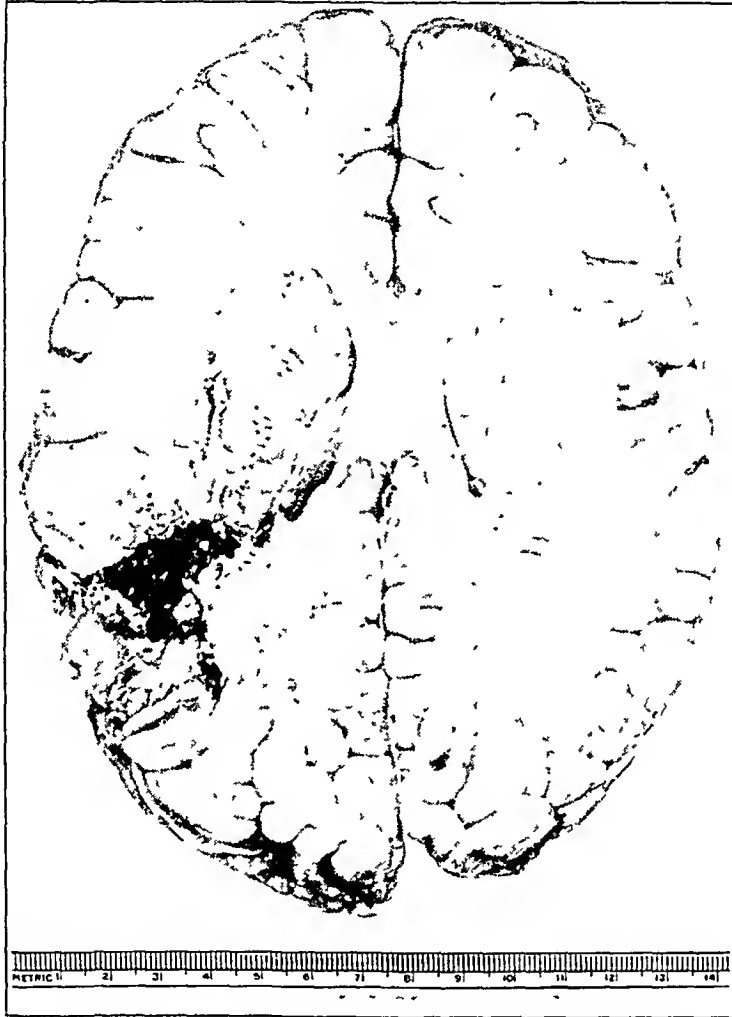


Fig. 2.—Hemorrhage in the left parietal lobe and extensive softening in adjacent tissue.

Brain: The brain was large and weighed 1,520 Gm. The dura and leptomeninges were somewhat dry and congested. There were several small subarachnoid hemorrhages. The cerebral convolutions were flattened and broad. The left hemisphere was more voluminous than the right. There was a fairly extensive, but poorly defined, softening in the left parietotemporal region; it included areas 40, 41 and 42 of Brodmann. The vessels forming the circle of Willis and its branches were thin walled and of average caliber. The internal carotid and middle cerebral arteries were dissected. The posterior branch of the left middle cerebral artery was filled with a soft red thrombus, which completely occluded the vessel. The anterior branch and the corresponding vessels on the right were empty. There were extensive, more or less symmetric subarachnoid hemorrhages in the cerebellum (fig. 1). The extravasations of blood extended slightly into the parenchyma. The source of the hemorrhage could not be determined.

Dissection of the cerebral hemispheres disclosed a large, firm blood clot in the left parietal region (fig. 2). The hemorrhage was well circumscribed. The tissues adjacent

to the clot were extremely friable. Almost the entire middle third of the left hemisphere showed areas of ischemic and hemorrhagic necrosis (fig. 3). The left frontal pole and the left occipital lobe were uninvolved. The left lenticular nucleus was dotted with numerous small hemorrhages. The adjacent anterior limb of the internal capsule was somewhat soft. The posterior limb, the caudate nucleus and the thalamus appeared intact. The cortex and subcortex of the left parietal lobe were very soft. A circumscribed hemorrhage lay close to the wall of the posterior horn of the lateral ventricle. The ependyma was intact. The area of infarction was smaller in ventral levels. Relatively large portions of the basal ganglia showed no gross changes at these levels. The infarct extended into the left temporal lobe, but the temporal pole was intact. The occluded vessel may be identified in the sylvian fissure in figure 4. All other vessels were narrow, thin walled and empty. The right hemisphere was free from gross lesions.

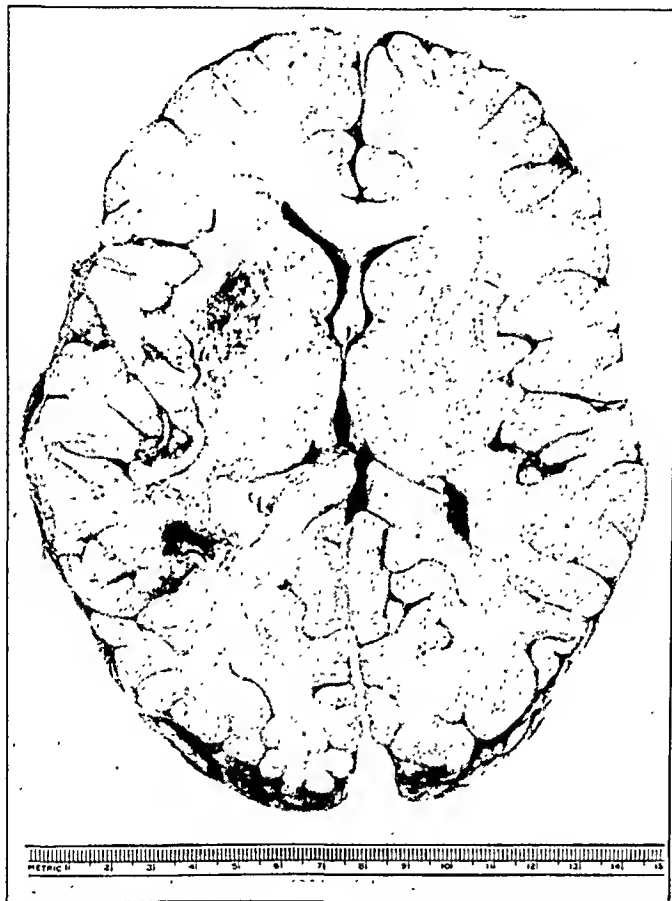


Fig. 3.—Areas of hemorrhagic and ischemic necrosis in the left cerebral hemisphere.

Microscopic Examination.—Brain: Histopathologic studies were made of sections from the left frontal, paracentral, parietal and occipital regions; the right frontal, paracentral, parietal and temporal areas; the neocerebellum, the mesencephalon, the medulla oblongata and the occluded branch of the left middle cerebral artery. The following staining technics were employed: hematoxylin and eosin, thionine, phosphotungstic acid hematoxylin and the Weil, Davenport, Heidenhain and Perdrau stains.

The leptomeninges were everywhere thin but showed areas of decided focal fibrosis, especially over the right and left paracentral lobules. There were marked hypervascularity and congestion. Small subarachnoid hemorrhages were present in all sections except those of the medulla oblongata. The hemorrhages were evidently recent, as the erythrocytes were well preserved and there was little hemosiderin pigmentation.

The occluded branch of the left middle cerebral artery had an exceedingly thin wall, apparently free from disease. It was filled with a thrombus, which had partially contracted away from the vessel wall, carrying the endothelium with it. A small series of interrupted

serial sections was made of the occluded vessel. In some areas red blood cells lay between the detached thrombus and the injured wall of the vessel. The erythrocytes composing the thrombus were for the most part well preserved. There was only slight hemosiderin pigmentation. The red cells were closely packed, and there was relatively little formation of fibrin. White blood cells were not numerous. There was a certain amount of lamination at the periphery of the clot. In one area there was a small group of fibroblasts. Nearby were a few narrow empty channels lined with endothelium.

Parenchymal vessels were greatly engorged. The capillaries in the gray matter were hyperplastic. Many small hemorrhages were observed in every section except those of the medulla oblongata. In the left parietal lobe, where larger extravasations of blood appeared, the ruptured walls of vessels were demonstrable. Ruptured vessels were also noted in the right parietal lobe. A few small vascular channels in various areas were filled

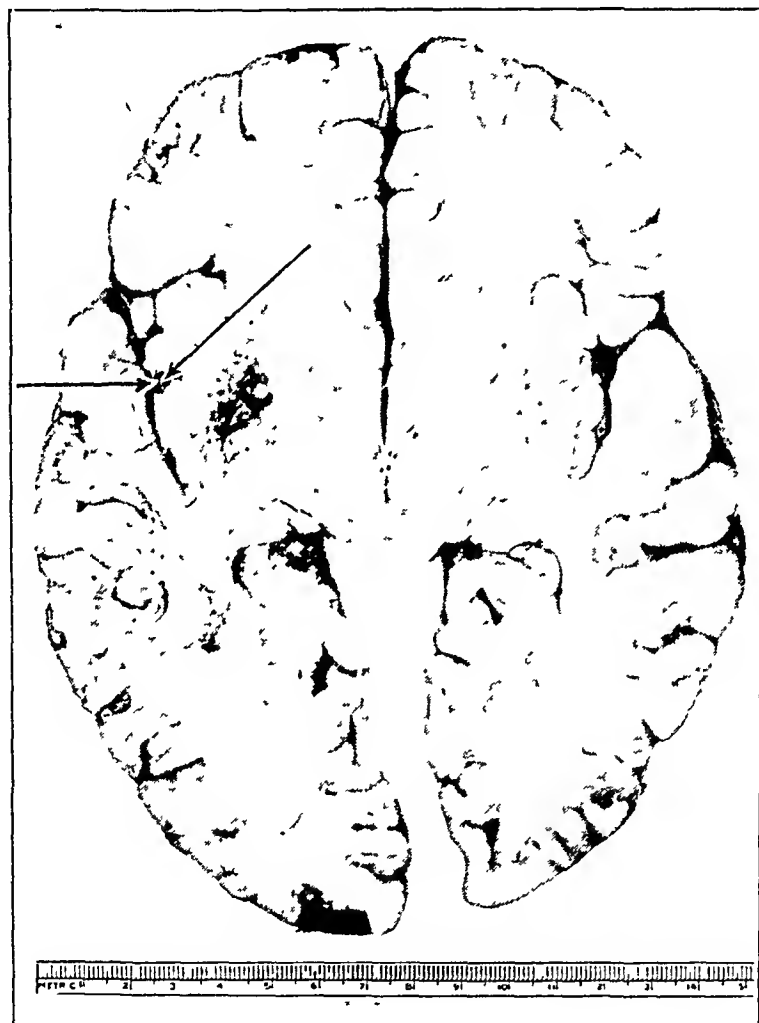


Fig. 4.—Hemorrhagic infarct in the left lenticular nucleus and infarction of the left temporal lobe. Arrows point to the occluded left middle cerebral artery.

with hyaline thrombi. Occasional arterioles showed proliferation of their lining cells. A number of capillaries, and larger vessels too, were lined with swollen endothelium. There were rare slight perivascular accumulations of granulocytes, round cells and pigmented reticuloendothelial cells.

A section from the left parietal lobe included a portion of the hemorrhagic infarct. Scattered throughout the section were irregular areas of tissue rarefaction, where myelin sheaths and nuclear elements were reduced in number. A few of these pale, spongy areas lay in the vicinity of engorged blood vessels. There was conspicuous loss of nerve cells in the areas of cortex near the superficial hemorrhages. The remaining neurocytes were severely damaged. They were usually pale and shrunken or were undergoing lysis. There was no proliferation of the glia or mobilization of polymorphonuclear leukocytes. Gitter cells were not seen. A few macroglia cells had hypertrophied, folded nuclei. They thus resembled Alzheimer glia cells. Some gliocytes were disintegrating. Edema was evidenced by many "pericellular spaces" and dilated Virchow-Robin spaces.

In other areas lamination and polarity of nerve cells were only fairly well preserved. There were numerous scattered empty spaces. The majority of neurocytes showed ischemic, homogeneous changes. Apical dendrites were notably thickened in many instances. Some of the ganglion cells had pale, more abundant cytoplasm, but even these rarely contained any Nissl substance. Cytolysis was sometimes observed. There were a few shadow cells.

Proliferation of gliocytes was slight except in the mesencephalon. In the tectum of the midbrain, the microglia and macroglia cells were hypertrophied, and three mitotic figures were observed. A minute focus of gliocytes and small round cells was noted in one peduncle.

In the left frontal lobe there was scattered marginal fibrillary gliosis, and one large warty nodule of glia fibrils projected into a sulcus. Unusually large ependymal granulations were observed in the posterior horn of the left lateral ventricle. In the aqueduct a single exceptionally large glial nodule projected into the cavity from the floor. It was attached by a narrow band of ependymal cells, so that it resembled a small tumor rather than a granulation. A few small, shallow granulations were noted in the lining of the inferior horn of the right lateral ventricle.

Myelin sheaths were intact except in the parietal lobe, where the number was reduced in the rarefied spongy areas. The sheaths that remained in these areas were widely separated and occasionally showed slight focal swellings. Some of the destruction of myelin occurred at the junction of the gray and the white matter, so that there was focal destruction of U fibers in such regions.

Other Organs: Sections from the abdominal and thoracic viscera showed widespread focal congestion and stasis. In the lung were a number of small hemorrhages and early bronchopneumonia. There was slight infiltration with lymphocytes and plasma cells in the interlobular connective tissue of the liver. In none of the sections was there any evidence of disease of the vessel walls.

COMMENT

The sudden onset of a cerebral accident in a young, well preserved person with no objective evidence of generalized vascular disease is rare. The history of previous good health, equivocal neurologic signs at the time of admission, absence of injury to the head and almost acellular spinal fluid make the probability of occlusion of the left middle cerebral artery with cerebral infarction the most reasonable diagnosis.

This case, and the one reported by Malamud and Boyd, are apparently unique in that such extensive, grossly demonstrable damage occurred in the brain. In general, in most of the cases of fatal acute catatonic excitement reported in the literature only microscopic changes, or none at all, were present.

In our case the small areas of loss of nerve cells, minor pathologic alterations in the neurocytes and slight glial reaction, while similar to changes reported in other cases of acute schizophrenia, are not considered significant.

The vessel walls did not appear diseased. The scattered vascular "blow-outs" in both cerebral hemispheres may well have been an expression of cerebral vasomotor hyperactivity. If true, this might substantiate the theory of von Braunnühl⁹ and Spielmeyer¹⁰ that functional circulatory disturbances operate as an important factor in acute catatonic excitement. The factors responsible for the thrombosis of the posterior branch of the left middle cerebral artery in our case were not demonstrable.

The clinical features of our case, together with the fatal termination, correspond closely to those in many other recorded cases of "schizophrenic death."

SUMMARY

A 22 year old man with schizophrenia died twelve days after the onset of an acute catatonic episode and five days after the sudden development of right hemiplegia. Negativistic and assaultive behavior, lability of mood, colorful and bizarre hallucinatory and delusional mental content, expression of guilt feelings, confusion and disorientation were outstanding features of the psychosis. Manifestations of vasomotor lability comprised the striking physical observations prior to the development of

the neurologic signs. At autopsy thrombosis of the left middle cerebral artery was observed. There were hemorrhage and infarction in the left parietotemporal region and extravasations of blood in the subarachnoid spaces and the parenchyma of the cerebellum. The underlying cause of such extensive anatomic damage was not ascertained. The clinical resemblance of this case to other reported instances of "brain death" associated with catatonic schizophrenia is noted. The explanation of the lethal vascular accident is thought to lie in functional circulatory changes often associated with this form of mental illness.

Glen Lake Sanatorium, Oak Terrace, Minn.

St. Elizabeths Hospital.

DR. H. DOUGLAS SINGER'S CONCEPT OF THE PSYCHOSES

IRENE C. SHERMAN, M.D., Ph.D.

AND

SAMUEL B. BRODER, M.D.

CHICAGO

Dr. H. Douglas Singer was one of the leading psychiatrists in this country, so that it now seems fitting to present some of the psychiatric concepts he had formulated during the later period of his life. We, who were members of his staff for many years, have attempted in this paper to give a brief outline of the development of his ideas concerning the psychoses. All of the views herein presented are in essence those of Dr. Singer. So far as possible, his own words have been retained.

Since the opening of the Psychiatric Institute of the University of Illinois College of Medicine, in 1931, it has been customary to present a case history of a patient at the weekly staff meeting. After the reading of the history by a member of the staff, there followed a general discussion of the problems involved. Dr. Singer was practically always present at these meetings, and his interpretations of the facts at hand, as well as his general comments on matters of psychiatry, were always particularly stimulating to the group. His keen criticism, his stress on logical thinking and his wisdom in demanding that basic pathologic processes be sharply separated from precipitating environmental factors were outstanding in his approach to an understanding of mental illness.

Even before the advent of shock therapy and the growing realization of the role of the integrative machinery of the body, particularly the autonomic nervous system, in the psychoses, he began to formulate his theory of the psychosis as a disturbance of this machinery. As will be seen later, he finally adopted the point of view that manic-depressive psychosis and schizophrenia have a similar location pathologically in the autonomic integrating centers.

At the Psychiatric Institute there are available stenographic notes of the discussions on some 400 case histories which were presented at staff meetings, with final diagnoses made by Dr. Singer. In the belief that his statements are of inestimable value for an understanding of mental disease, an attempt is here made to trace the development of his theories of the psychoses during the period that he was director of the institute, from 1931 until his death, in 1940, and to summarize briefly his point of view regarding the various psychoses.

SCHIZOPHRENIA

In the early staff discussions, patients with schizophrenia simplex were found to show characteristically a progressive loss of interest and affect over a number of years, but not necessarily acute psychotic disturbances or evidence of splitting. Interest was considered a response of the organism as a whole and a matter of affectivity as this arises from drive or energy which is vegetative in origin. Interest thus was regarded as a matter of body organization. Although the loss in schizo-

From the Department of Psychiatry of the University of Illinois College of Medicine, and the Psychiatric Division of the Illinois Neuropsychiatric Institute.

phrenia simplex does not concern intelligence, with diminution of emotional drive, which makes the expression of intelligence feasible, intelligence is not used to advantage.

The cause of schizophrenia simplex was at first regarded as an active disease process which is progressive and destructive, the loss becoming more evident as greater demands are made on the organism, until finally there is reduction to a low level of response, manifested by such activities as appetite and masturbation. Thus a deterioration occurs, a progressive chronic dementia, which may also characterize hebephrenic schizophrenia in some instances, although the latter has other features which distinguish it from schizophrenia simplex, features which comprise the descriptive term hebephrenic and may include an ultimate condition of stasis.

During this period (1933) the classification of hebephrenia was sometimes applied (1) to cases in which there was a constitutional defect in the form of passivity and a fundamental lack of drive from early life, (2) to cases in which it seemed justifiable to infer that a progressive disease process was present, producing a loss of mental function and (3) to cases in which there was neither a lack of fundamental drive nor a disease process, but a poor reaction to a situation. This varied usage of the term hebephrenic illustrates clearly the point of view that the form of the psychosis tells nothing of the underlying etiologic factors.

In 1934 it was indicated that in many cases of dementia simplex a structural defect in energy is evident from the start; this defect is the main feature of simple schizophrenia and shows itself in lack of adaptation when the person is no longer protected and has to face definite responsibilities. It is then that his inefficiencies become more evident. This behavior of a person who is poorly constructed to face his difficulties is not due to a disease but is a reaction between his constitution and the environment. He is a biologically inefficient person, and although he may not change, the demands on him may do so. At this time, however, the belief was expressed that, in addition, there is a progressive degenerative change which manifests itself in greater isolation and a let-down in the ability to deal with the reality situations of adult life, due to loss of energy or drive. The latter condition is dementia praecox in the true sense of the word, for it is a dementing process that results in destruction, a progressive loss and not merely an original constitutional deficiency. Thus dementia simplex has an organic substratum and few psychogenic features.

In the paranoid form of schizophrenia, too, the main feature was considered a constitutional defect in the quality of energy, which is the basis of the patient's difficulties in meeting his conflicts and which results in the use of the typical mechanisms of rationalization and projection. As early as 1932 the form of this psychosis, as of all psychoses, was thought to evolve from the type of personality. Thus the paranoid condition is a defect plus a superstructure of psychogenic factors which are expressed as a disturbance of personality. It may be said that the paranoid person is oversocialized. He shows an intense subordination to convention. Such a patient is able to utilize the mechanism of projection because he is endowed with good energy quantitatively, although not qualitatively. This permits of aggression and the blaming of others, rather than the adoption of a passive attitude of self blame for his inefficiencies.

In practically every case of the catatonic form of schizophrenia the presence of a disease process was suggested. The patient does not show voluntary withdrawal from the world but is overwhelmed by an illness which affects the vegetative mechanisms. Although the behavior is catatonic from the descriptive standpoint, this term is in no sense explanatory of the process which gives rise to it. one

which may produce reversible or irreversible and permanent changes. When the process is reversible, the machinery of the higher levels is shut off but not damaged permanently. Thus it is possible to have schizophrenia without dementia.

The catatonic excitement is accompanied by withdrawal from and lack of interest in the outside world; the behavior is not related to the surroundings. This is in contrast to manic excitement, in which the patient manifests an overinterest in the outside world; the pattern of his behavior is controlled by the surroundings; his mood is happy, and he shows an interest in sensory perceptions. The catatonic person, on the other hand, is not happy and shows no interest in his surroundings.

Dr. Singer rejected the idea that schizophrenia is a regression to a more infantile type of behavior, due to a shutting-off of the machinery for reacting at higher levels. He expressed the belief that there is overdevelopment in the other direction, an oversocialization, expressed by the development of too many taboos. Unable to express things in the way he wishes, the patient carries out his wishes in a more primitive manner (1934).

Schizophrenia means splitting at a high level of response. The split is shown, for example, by hallucinations, in which voices are described as coming from without, and by features that are odd and do not seem to be fitting or understandable to the observer, and perhaps to the patient, and that require interpretation or explanation at a psychic level. The verbal expressions are not consistent with the emotional responses or the muscular activity, and this inconsistency is further evidence of a split. Many of the responses are due to internal stimulation, and because they are symbolic they seem odd and inexplicable.

In many cases of schizophrenia there is no history which suggests a defect in constitution. The history may indicate that a change of personality took place abruptly. This was interpreted to mean that an illness had occurred, damage had resulted and, as a result, activity, accomplishment and function were reduced to a lower level. At this time (1934) Dr. Singer stated that he had no conception of the location of the disease process. The condition, however, was regarded as an organic dementia belonging to the group of dementia praecox, for it represents an actual disease process and a progressive loss of mental efficiency.

The term schizophrenia does not signify an entity and is not necessarily descriptive of a disease, but denotes a form of behavior of a psychogenic nature. A situational reaction, for example, is not a disease but may be schizophrenic in the type of behavior shown, the reaction being the patient's way of meeting the threatening situation. Thus schizophrenia is a formal descriptive term for behavior that may occur as the result of a disease process or of a maladjustment to the environment, with personality difficulty. From the beginning of 1934, therefore, the case in which the history suggests that a disease process has occurred at some time during the patient's life has been classified as one of "schizophrenia, organic type." The term schizophrenia is preferable to that of dementia praecox because the condition is not a dementia in the sense of intellectual loss and does not necessarily occur at an early age. In those instances in which the illness was obviously a reaction to the environment, the condition was classified as "schizophrenia, psychogenic type."

Late in 1935 Dr. Singer referred to a given case of schizophrenia as a vegetative disturbance in the same sense that the manic-depressive psychosis is a vegetative disorder. This was the precursor of his theory, later to be advanced,¹ that both

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the organic schizophrenic psychosis and the manic-depressive psychosis are pathologically the same, namely, disorders of the autonomic nervous system, and that they differ symptomatically because of the type of person who is ill.

It was contended that schizophrenia, psychogenic type, is a disturbance in behavior, schizophrenic in nature, not due to bodily illness. The symptom picture of schizophrenia may be psychogenic if it is a reaction motivated from a higher level (1936). It was stated, however, that the psychoneurosis is due to a relative constitutional weakness, probably a defect in the energy available for reaction, which makes the person less capable of adjusting to external conditions. Although the essential feature of a psychoneurosis is a maladjustment between the person and his environment, and therefore is primarily situational and a personality problem, the failure in adaptation may be extreme enough to necessitate the patient's removal from the environment, so that by definition it may be classified as insanity, which means a condition producing incapacity to manage one's affairs acceptably to society.

When the illness is organic, at a lower level, the manifestations must be studied with the purpose of finding what relation they have to the actual behavior. A person who is reacting at a higher level has insight. Even a psychotic person with schizophrenic hallucinations and ideas of reference knows that these are not real and has insight to that extent. The monotony of ideas in schizophrenia is due to the fact that they do not arise from higher levels of consciousness. The patient does the unexpected; for example, he strikes another patient for no reason. There is no clue to this behavior. The act does not occur because of anything the other person did; it comes from within and is not related to the world outside. Thus schizophrenic behavior is characteristically unpredictable. The pattern is monotonous and repetitious because the motive forces, which come from within, are relatively unchanging, as compared with the rapidly changing stimuli from the outside (1936).

In cases of the organic type the loss is of the emotional reactions, such as initiative, interest and drive. Emotion is a manifestation of energy in the body, and the term dementia was used to mean merely a loss of this energy, although it was recognized that the term dilapidation was preferable. The same sort of loss may occur in the presenile psychoses and in dementia paralytica, in which there is in addition an intellectual loss.

In 1937 psychosis was defined as a disturbance of the autonomic nervous system, which produces a change in the autonomic regulation of activity. Inflammatory and other conditions affecting the central integrating mechanisms may also cause damage to the autonomic machinery, which will account for the emotional changes sometimes associated with dementia paralytica and other diseases primarily of the central nervous system.

Deterioration is due to a disease process in the central autonomic centers, an actual structural change which is irreversible. An active disturbance in these centers will also account for swings of excitation when they occur. These swings may be either manic or schizophrenic in form, depending on the personality.

It was emphasized that the term schizophrenia merely denotes an exaggeration of a personal mode of reaction brought about by stress, which may occur as damage to the integrating mechanisms or may be the result of overwhelming difficulties in the situation. The former constitutes a psychosis; the latter, a psychoneurosis.

After the sorting out of cases of organic schizophrenia, the primary defect at the vegetative level (poor energy but no deterioration) in cases of simple schizo-

phrenia was stressed more and more, and finally the label "simple schizophrenia" was limited to a condition with an obvious defect in constitution. Late in 1938 Dr. Singer stated that it seemed to him worth while to keep the term simple to refer to a constitutional defect which shows itself all through life and to restrict the other names, like hebephrenic, catatonic and paranoid, to refer to those conditions that are not inherited but are due to something that has happened since birth. This concept that simple schizophrenia is a primary defect at the vegetative level (energy), with nothing added, was a departure from the earlier point of view that it is a deterioration due to a disease process. It was recognized, however, that a constitutionally defective person may have superimposed on his defect added stress in the form of actual damage within the organism. Schizophrenia of this type was now classified as organic, the subgrouping depending on the characteristic features of the behavior.

In summary, the schizophrenias may be classified in three types: (1) a defect, which includes simple schizophrenia and some paranoid schizophrenias; (2) an organic disease process, in which the symptom picture may be that of the hebephrenic, catatonic or paranoid form, depending on the person who is ill, and (3) a psychogenic disorder in which, again, the form of the illness may be any of the aforementioned three types. These conditions are properly classified as psychoneuroses.

MANIC-DEPRESSIVE PSYCHOSIS

In 1934 the view was expressed that a manic or depressive reaction is a vegetative upset which influences the higher levels secondarily. The depression, for example, is not a withdrawal but a change in the actual vegetative activity of the body itself. There is a forcefulness about the mood which leads the patient to adopt definite ideas and reactions. In the manic condition, moreover, the expressions are frank and appropriate, and the patient is conscious of their meaning, in contrast to schizophrenia, in which the expressions are unintelligible to the observer, and probably also to the patient, because they are expressions of something unconscious. In a depression the mood may lead the patient to justify it by the use of ideas of self condemnation. The patient utilizes every possibility to express his feelings; this is a secondary reaction through the conscious levels. When chances for adjustment are diminished, doubts and fears apart from the illness will be strongly in evidence. Any one in such a depressed mood will be preoccupied with his own ideas of what is unpleasant and depressing. Such thoughts, however, do not cause the depression.

It was stressed at this time that the term manic-depressive psychosis, like the term schizophrenia, describes not a disease, but a reaction or mode of behavior, the basis of which may be a number of things. The disorder may, for example, be precipitated by an acute infectious illness which disturbs the constitution, or it may arise as the result of a toxic process.

Shortly thereafter Dr. Singer's concept of the manic-depressive reaction was broadened: It was now considered that the condition is a reflection of the personality, and thus may be associated with and characterize any type of illness. A patient with cerebral arteriosclerosis, for example, may manifest typical manic features in his psychosis, or one with dementia paralytica may be depressed. Yet the terms "manic" or "depressed" tell nothing of the underlying illness.

Thus a diagnosis has not been made when a psychosis is labeled "manic-depressive." Some disease may be present which produces a change in the general metabolic activity of the body, or there may be merely an oscillation of mood

beyond the normal limit. The manic-depressive syndrome, however, is not always vegetative in character, since it is merely a product of the personality. But a vegetative illness is not a personality disorder, although one may observe psychogenic features therein, such as phobias, which are personality disorders, that is, variations at a higher level depending on something in the experience of the person. Psychogenic depression does not show the same retardation as the manic-depressive depression, and there is an element of anxiety, which is due to conflict. In most situations of depression in which there is severe agitation one finds a rigid personality. Thus the attitudes of the patient during the depression give it a typical coloring. The same element of personality is involved both in the disturbances of mood which are psychogenically determined and in those which are the result of deranged bodily activity. One must know, therefore, how the depression came about, what it means in the functioning of the body and what is the nature of the disturbance. A true manic-depressive depression involves all functions.

In 1937 Dr. Singer stated that the swings of mood brought about by environmental factors should be classed as psychoneuroses. In these instances the person is reacting to some conflict with the environment—to demands of the environment which arouse emotion. The stress in these instances is psychogenic, and the psychogenic factors in experience determine the form in which the disturbance of mood is expressed. Nevertheless, environmental factors also play an enormous part in precipitating vegetative disturbances in persons who are liable to them, and disturbances thus psychogenically initiated may occur in the psychoses. Sometimes the vegetative imbalance is so great that anything will precipitate a disturbance. There is a tendency to emotional upset which must be regarded as part of the build of the person, in addition to other bodily factors which may precipitate mood swings.

To question whether one is dealing with a manic-depressive disease or with a reactive excitement or depression is only another way of asking the level of the disturbance. Swings in mood may occur only during periods of bodily stress, a stress not related to the environment, which lowers bodily resistance and initiates an upset. A manic-depressive depression is a disturbance on the vegetative level. Often it is extremely difficult to differentiate a psychoneurosis from a vegetative disturbance, for there may be pathologic mood swings in persons who also are neurotic. One striking feature is the monotony in the vegetative disturbance. Most reactive or psychoneurotic persons can be distracted and the agitation of the depression will subside, but this cannot be accomplished with a person who has a more fundamental disorder.

In 1934 the psychosis had been defined as a state of mind that is pathologic in the sense that it is excessive or too prolonged or involves a distortion of reality.

The following year Dr. Singer again indicated that a disturbance, even when precipitated from the outside, may be psychotic in the sense that it is pathologic in degree and duration. He again stressed, however, that all psychotic conditions are reactions, not diseases; they are behavior characteristics of the person who is ill. Whether a condition is manic or schizophrenic, for example, is merely a psychologic or personality classification.

Late in 1937, after the advent of shock therapy and the recognition of the possible role of the autonomic nervous system in mental disorders, the manic-depressive psychosis, like all psychoses, was defined as a disturbance of the central autonomic integrating mechanisms, perhaps pathologically the same as schizophrenia, and differing from it only in form because of differences in the person who

is ill. Whether the patient behaves as a schizophrenic or as a manic-depressive person makes no difference if the disorder occurs at a given biologic level as the result of the same type of bodily chemical change.

Although psychosis was now defined as a disturbance of the autonomic nervous system, the idea was still retained that the main determining factor in the form of the psychosis is the person who is ill, and that the terms "manic-depressive" and "schizophrenic" are merely descriptive of the expressed behavior, not diagnoses of the underlying disease process. Nevertheless, manic-depressive psychosis was now regarded as an organic illness, of central origin, involving the whole organism. The diagnosis is not merely a matter of the recognition of a specific type of persistent oscillation of severe degree in the autonomic adjustments. Instead of showing the normal mood swings, such persons exhibit a tendency toward greater degrees of oscillations, which last for a long time. These swings occur in persons who have such a constitutional makeup, for when the autonomic regulation is inferior in quality, there are more pronounced effects than when the organization is more adequate. Persons who cannot handle ordinary trauma show excessive reactions—to infections or to psychologic stress—which may cause a disturbance of equilibrium beyond the normal range. Such swings occur in both manic-depressive and schizophrenic conditions.

After attacks of what most people call manic-depressive psychosis, there may be deterioration (loss of energy), although this is not common. Such deterioration is due to irreversible damage in the mechanisms of integration, and is obviously organic. It is probably identical with the illness which sometimes appears as a schizophrenic reaction. Disturbances in autonomic integration must result in disturbances of mood. When the expression of mood is frank and extrovert, the condition is classified as manic-depressive psychosis, and when it is introvert and symbolized, as schizophrenia. The typical manic-depressive psychosis may more adequately be labeled a periodic autonomic imbalance, a designation which defines the illness in terms of the underlying pathologic process. Likewise, it was anticipated that the pathologic basis of schizophrenia would some day be described, and that schizophrenia, too, could then be given a name which would connote the basic underlying condition.

30 North Michigan Boulevard.

6 North Michigan Boulevard.

PATHWAYS FOR PAIN FROM THE STOMACH OF THE DOG

OSCAR J. BALCHUM, M.Sc.

AND

H. M. WEAVER, Ph.D.

DETROIT

For purposes of description the sensation of pain may be subdivided into two main categories: viz., somatic pain, produced by the noxious stimulation of the peripheral somatic nerves, and visceral pain, experienced after the appropriate stimulation of a viscus. In addition to these more common categories, a third variety of painful sensation, commonly designated as referred pain, is characterized by the fact that the painful sensation is interpreted by the subject as originating from the surface of the body, although it is known to be the result of the noxious stimulation of a viscus far removed from the painful area.

It is generally agreed that stimulation of the parietal pleuroperitoneum by scratching or rubbing results in sensations of pain (Lennander¹; Alvarez²; Morley³), whereas stimulation of the visceral pleuroperitoneum is painless (Lennander¹; Capps and Coleman⁴; Alvarez²). Most authors have expressed the belief that the gastric mucosa is insensitive to painful stimuli (Carlson and Braafladt⁵; Alvarez²). On the other hand, Boyden and Rigler⁶ reported that they produced pain by stimulating the gastric mucosa of human beings with a faradic current. Although deeply seated, the pain was "projected" to the skin, and these painful areas tended to shift with changes in position of the electrodes within the stomach.

It is believed that traction on the mesenteries is a stimulus adequate for the production of pain (Neumann⁷; Breslauer⁸; Adams⁹; Lebendenko and Brjusowa¹⁰; Alvarez²). Meyer¹¹ and Alvarez² stated that neither distention nor

From the Department of Anatomy, Wayne University College of Medicine.

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(Footnotes continued on next page)

contraction of a viscus will cause pain unless the mesentery is stretched. Using the dilatation of the pupil as an index of visceral afferent activity in cats anesthetized with chloralose (a compound of chloral hydrate and dextrose), Irving, McSwiney and Suffolk¹² stated that the threshold pressure for visceral afferent activity, after distention of the pylorus with a balloon, could be increased by at least 75 mm. of mercury by painting the pyloric mesenteries with cocaine. Brüning and Gohrbandt,¹³ while admitting that traction on the mesenteries will cause pain, stated that distention of the viscus is the more important stimulus. The results of these experiments indicate that traction on the mesenteries can initiate visceral afferent activity and that the nervous activity resulting from the distention of a viscus may be due in part, or in whole, to traction on its mesenteries.

The great majority of workers believe that distention of a hollow viscus is a stimulus adequate for the production of pain (Brüning and Gohrbandt¹³; Fröhlich and Meyer¹⁴; Kappis¹⁵; McDowell¹⁶; Lebendenko and Brjussowa¹⁰; Alvarez²). Bloomfield and Polland¹⁷ introduced balloons into the stomachs of human beings and inflated them with air. The intragastric pressures rose to and remained at 40 mm. of mercury, and discomfort and pain were felt by the subjects after 200 to 500 cc. of air had been introduced. Hurst,¹⁸ Payne and Poulton¹⁹ and Morley³ expressed the belief that the pain which follows distention of a hollow viscus is caused by stretching of its sensory nerves. Spasm of the gastrointestinal musculature (Müller²⁰; Ryle²¹; Fröhlich and Meyer¹⁴), as well as the increased tension on the muscular coat of a distended viscus (Hertz²²), is thought to be stimulus adequate for the production of pain.

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POSSIBLE PATHWAYS FOR VISCERAL PAIN

Although the vagus nerve does contain visceral afferent fibers below the level of the diaphragm, it is generally believed that this nerve is not concerned with the transmission of pain from the abdominal portion of the alimentary canal (Langley²³; Ranson²⁴; Kappis²⁵; Breslau⁸; Alvarez²⁶; Duschl²⁷; Cannon²⁸). The studies of Heinbecker and O'Leary²⁹ indicated that the vagus nerve, below the level of the diaphragm, is chiefly motor in function.

It is the consensus that the greater splanchnic nerve serves as the main pathway for painful impulses originating within the upper portion of the abdomen (Kappis¹⁵; Duschl²⁷; Cannon²⁸; Alvarez²). Ross³⁰ expressed the belief that the sensory fibers in the greater splanchnic nerve which supply the stomach are associated with the fourth, the fifth and, possibly, the sixth thoracic segment of the spinal cord, whereas Ranson and Billingsley³¹ stated the opinion that the sensory fibers in the greater splanchnic nerve enter the spinal cord via the posterior roots of the sixth to the ninth thoracic spinal nerve. Edgeworth³² stated that the large medullated (probably sensory) fibers originating in the abdominal viscera and traveling by way of the greater splanchnic nerve enter the spinal cord mainly through the posterior roots of the eleventh thoracic to the second lumbar spinal nerve. Bain, Irving and McSwiney³³ stimulated the central stump of the right greater splanchnic nerve in cats anesthetized with chloralose in which the spinal cord had been transected between the fifth and the sixth thoracic segment. Dilatation of the pupil, described by these workers as a very sensitive index of visceral afferent activity, was evident. However, after the right sympathetic trunk had been transected between the levels of the sixth and the seventh thoracic vertebra, stimulation of the right greater splanchnic nerve failed to cause dilatation of the pupil, although stimulation of the left greater splanchnic nerve was still effective. These investigators reported, further, that the spinal cord had to be transected at or above its third thoracic segment in order to eliminate, by transection of the spinal cord alone, the dilatation of the pupil caused by stimulation of the greater splanchnic nerve. These experiments indicate that some of the

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sensory fibers in the greater splanchnic nerve travel cephalad in the sympathetic chain and enter the spinal cord as high as its third thoracic segment. Cannon²⁸ reported that stimulation of the greater splanchnic nerve and of the upper lumbar portion of the sympathetic trunk is followed by actions which are indicative of pain.

Irving, McSwiney and Suffolk¹² stated that the threshold pressure for visceral afferent activity during distention of the stomach varied from 10 to 60 mm. of mercury. It appears from their experiments that the visceral afferent impulses initiated during distention of the stomach and during traction on the gastric and duodenal mesenteries reached the higher centers by way of both the vagus and the greater splanchnic nerve. Lebendenko and Brjussowa¹⁰ found that the pain resulting from distention of the stomach of the dog could be abolished by a posterior rhizotomy extending from the fourth thoracic through the third lumbar level of the spinal cord. These investigators reported, further, that transection of the spinal cord at its fifth thoracic segment, bilateral transection of the sympathetic trunk at the level of the fifth rib and bilateral transection of the phrenic and vagus nerves did not abolish the pain produced by stretching of the gastric mesenteries. The investigators explained their inability to alleviate the pain produced by traction on the gastric mesenteries as due either to stimulation of the thoracic viscera by changes in pressure or to the presence of still another pathway for painful impulses, possibly associated with the aortic plexus.

MECHANISM OF REFERRED PAIN

Many theories have been proposed in an attempt to explain the neurologic mechanism of referred pain. Ross³⁰ was one of the first to state that a diseased organ gives rise to two types of pain, viz., a deeply seated pain located directly over the organ, and a more superficial, better localized pain in areas far removed from the site of the diseased viscus. This investigator proposed the theory (which was original with Stürge³⁴) that irritation of the visceral terminations of the greater splanchnic nerve results in the passage of impulses to the posterior columns of the spinal cord, where they "diffuse" to the sensory fibers of the intercostal nerves. An "associated pain" is thus set up which is interpreted by the subject as having had origin along the distribution of the intercostal nerves which were involved. Head³⁵ suggested that the sensory and localizing powers associated with the body surface are far superior to those associated with the viscera. By what he termed a "psychical error of judgment," impulses which reach conscious levels from the "diffusion areas" of the spinal cord are interpreted by the person as having originated from the surface of the body rather than from the diseased viscus. Mackenzie³⁶ elaborated on Ross's theory of diffusion areas within the spinal cord. According to this worker, if the incoming nervous activity from the stimulated viscus diffuses onto and excites somatic afferent neurons, the subject interprets the pain as originating from the sensory terminals of the excited somatic neurons (the viscerocutaneous reflex). If, on the other hand, the incoming nervous activity diffuses onto and excites somatic efferent neurons, reflex rigidity of the somatic musculature innervated by that segment of the spinal cord results (the viscer-

34. Stürge, W. A.: The Phenomenon of Angina Pectoris and Their Bearing upon the Theory of Counter-Irritation, *Brain* 5:492, 1883.

35. Head, H.: On Disturbances of Sensation, with Especial Reference to Pain of Visceral Disease, *Brain* 16:1, 1893; 17:339, 1894; 19:153, 1896.

36. Mackenzie, J.: Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, *Brain* 16:321, 1893.

motor reflex). The sweating and pilomotor responses, frequently observed within areas of cutaneous hyperalgesia, were explained also by the concept of an "irritable focus."

Lennander¹ expressed the belief that referred pain is caused by stimulation of the sensory fibers of the somatic nerves by an irritated pleuroperitoneum, the latter resulting from contact with a diseased viscus. Morley³⁷ expressed the opinion that the dull, deep-seated pain located directly over a diseased organ results from tension on its walls, whereas the pain referred to the surface of the body is caused by irritation of the parietal peritoneum overlying the diseased viscus. According to this investigator, each somatic nerve supplies a strip of parietal peritoneum, the overlying skin and the intervening somatic musculature. Either nervous activity originating in the irritated peritoneum overlying a diseased viscus is misinterpreted as originating in the skin, or, what is more likely, there is actual diffusion of nervous activity within the spinal cord or the dorsal root ganglia from the sensory fibers supplying the peritoneum to the sensory fibers supplying the skin (the peritoneocutaneous radiation). The hypertonicity of somatic musculature, so frequently an accompaniment of referred pain, is brought about by activation of the anterior horn cells by nervous activity originating in the irritated peritoneum overlying the diseased viscus (the peritoneomuscular reflex).

Pollock and Davis³⁸ reported that the impulses initiated by the stimulation of the central diaphragmatic peritoneum traverse and enter the spinal cord over the trunk and the posterior roots of the phrenic nerves. Within the spinal cord, the impulses descend to the cells of the intermediolateral column of the eighth cervical and the first three thoracic segments. From this region the impulses travel through preganglionic sympathetic fibers, via the anterior roots, to the cervical sympathetic ganglia. These investigators stated:

From here postganglionic fibers travel to the skin, blood vessels, meninges and other structures, where by some vasomotor (?) or hormonal (?) process the sensory endings of the cerebrospinal system are stimulated and a sensory impulse travels over the ordinary cerebrospinal system, enters the spinal cord through the posterior roots and ascends to consciousness.

Hinsey and Phillips³⁹ questioned the existence of the elaborate pathway proposed by Pollock and Davis for the transmission of pain produced by stimulation of the central diaphragmatic peritoneum. These investigators reported that such pain is dependent on afferent fibers contained in the phrenic nerve only and that it is independent of afferent fibers in the vagus and intercostal nerves and of efferent fibers in the sympathetic pathways.

Lewis and Kellgren⁴⁰ injected a hypertonic solution of sodium chloride into the first lumbar interspinous ligament of a human being and stated that the patient experienced the same character and distribution of pain that he had had previously during attacks of renal colic. It was concluded from this study that there exists no special form of pain, referred or otherwise, and no special form of viscerosensory or visceromotor reflexes which can be considered hallmarks of visceral disease. According to these investigators, a common system of afferent nerves supplies the deep somatic and certain visceral structures and is responsible for all of the pain and the referred phenomena associated with visceral disease.

37. Morley, J.: *Abdominal Pain*, New York, William Wood & Company, 1931; footnote 3.

38. Pollock, L. J., and Davis, L.: *Visceral and Referred Pain*, *Arch. Neurol. & Psychiat.* **34**:1041 (Nov.) 1935.

39. Hinsey, J. C., and Phillips, R. A.: *Observations on Diaphragmatic Sensation*, *J. Neurophysiol.* **3**:175, 1940.

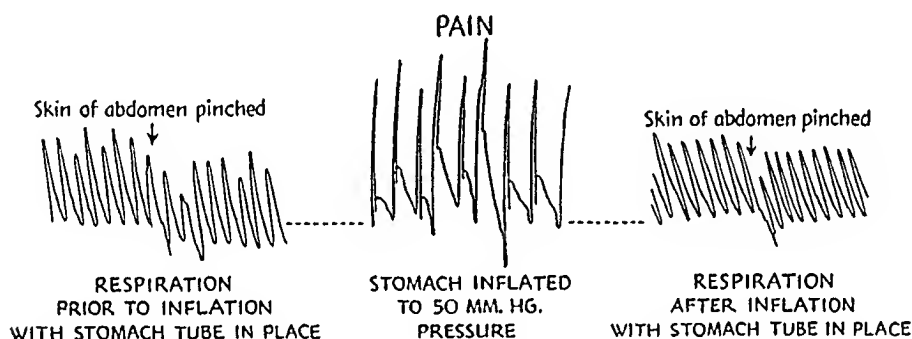
40. Lewis, T., and Kellgren, J. H.: *Observations Relating to Referred Pain, Viscero-Motor Reflexes and Other Associated Phenomena*. *Clin. Sc.* **4**:47, 1939.

EXPERIMENTAL PROCEDURE AND RESULTS

It is the purpose of this paper to record the results of an investigation in which the pathways for pain from the stomach of the dog were determined by surgical methods.⁴¹ Preliminary experiments indicated the necessity of a method for producing pain which was reproducible and in which the intensity of the stimulus could be calibrated accurately. The distention of the stomach with air by a balloon attached to a stomach tube and connected with an aneroid manometer proved to be satisfactory.

In the dog, it was found that a change in respiration was the only constant objective sign of the pain which follows distention of the stomach. This change was evident in the expiratory phase of respiration only and was of a peculiar step-like form (figure). Groaning and howling frequently accompanied the steplike form of expiration and aided in the final judgment as to whether or not the dog was experiencing pain.

The peculiar steplike form of expiration indicative of pain following distention of the stomach can be described as follows: The dog inhales deeply and quickly and then releases its breath in short spurts, or periods, of exhalation, halting momentarily between each period, so that, when recorded on the kymograph, the



Changes in respiration induced by painful distention of the stomach of the dog.

curve of the entire expiration resembles a row of steps. The graphs of Pollock and Davis³⁸ show a similar steplike type of expiration, but these workers did not indicate that it was regarded as a specific criterion of the presence of pain.

The apparatus used in the distention of the stomach consisted of a stomach tube, to the extremities of which were fastened a balloon and a T tube. A sphygmomanometer bulb, used to inflate the stomach, was attached to one arm of the T tube, and an aneroid manometer, calibrated in millimeters of mercury, was mounted on the other arm. The respiratory movements of the dog were recorded on smoked paper by placing on the dog's thorax a partially inflated rubber basketball bladder, which was connected to a tambour, on which was mounted a light aluminum stylus. The bladder was held in place by a metal arch, which was fastened to the sides of the table.

The actual procedure which has been employed in these studies can be illustrated by describing a typical experiment. A healthy dog of 10 to 15 pounds (4.5 to 6.8 Kg.) in weight was made to fast overnight, taken into a quiet room, fastened to the operating table and anesthetized with ether. When the stage of anesthesia was moderately deep, the stomach tube, with the balloon attached, was moistened with warm water and passed through the esophagus into the stomach. The dog was then allowed to breathe pure air until it responded, by a brief inhibition of respiration, to slight pinching of the skin of the abdominal wall. The balloon was then inflated rapidly by means of the sphygmomanometer bulb, and, as a rule, the intra-gastric pressure rose to about 35 or 40 mm. of mercury over a period of one to three minutes.

41. The suture material utilized in this experiment was furnished in part by Davis & Geck, Inc., Brooklyn.

The pressure usually remained at this level for an additional one-half minute, even though inflation was continued rapidly. In most cases the intragastric pressure then rose slowly to about 50 to 60 mm. of mercury, at which point the steplike expiration, indicative of pain, was evident (figure). The respiratory movements were recorded continuously throughout the experiment.

After establishment of the preoperative threshold for pain, one of a number of, or a combination of several, operative procedures was carried out (table). After enough time had elapsed for healing of the wound (this interval, which varied from one to three weeks, never reached the period required for regeneration of the transected nerves), the dog's stomach was again distended and its preoperative and postoperative thresholds for pain were compared. The postoperative threshold for pain was determined several times after each operation, a period of at least five days being permitted to elapse between inflations. Each animal was autopsied after its postoperative threshold had been established.

Since the animal's preoperative and postoperative thresholds for pain were recorded with the dog under light ether anesthesia, the question arose as to the possibility of error due to the influence of the anesthetic. The normal, or preoperative, thresholds were determined for 3 animals in the usual manner with the animal under ether anesthesia. Gastric fistulas were then constructed so that the stomach tube, with its attached balloon, could be inserted into the stomach directly without traversing the esophagus and in the absence of an anesthetic. The postoperative thresholds for pain were determined under these conditions and compared with the preoperative thresholds for the same dogs determined when they were under light ether anesthesia. The preoperative and the postoperative thresholds for pain were found to be practically identical. It is believed, therefore, that the state of anesthesia employed in these experiments had no effect on the thresholds for pain following distention of the stomach.

The question arose, also, whether or not a dog might become adapted to repeated distentions of its stomach and show progressively elevated thresholds for pain on subsequent inflations. Six dogs were subjected to such a procedure at frequent intervals for periods as long as seven months. No significant change in their thresholds for pain was observed.

It is conceivable that the venous and/or the arterial congestion within the stomach, resulting from the elevated intragastric pressure during distention of the organ, might alter the threshold for pain. As a test of this possibility, the veins draining the stomach were ligated in 2 dogs, and in 2 other dogs both the veins and the arteries were so treated. In no case was any difference evident between the preoperative and the postoperative threshold for pain following distention of the stomach.

Finally, the question arose as to the extent of the intragastric pressure required for secondary painful stimulation of the body wall and/or the structures and organs adjacent to the stomach. In 5 dogs the peritoneal cavity was distended with air by means of a hypodermic needle inserted through an anesthetized area of the abdominal wall. The peculiar steplike expiration, indicative of pain, appeared at pressures between 105 and 110 mm. of mercury in all cases. These experiments indicate that at intragastric pressures up to approximately 105 mm. of mercury the resulting pain is due to the distention of the stomach, whereas during intragastric pressures above this level the pain originates in the body wall and/or the structures adjacent to the stomach.

No significant change could be detected in the threshold for pain produced by distention of the stomach after either unilateral or bilateral transection of the vagus or the phrenic nerve in the cervical region or of the phrenic nerve within the thorax (table). Neither left unilateral nor bilateral transection of the sympathetic trunk just caudad to the origin of the greater splanchnic nerve (table) produced any change in the threshold for pain following distention of the stomach.

Results of Determination by Surgical Methods of Pathways for Pain from the Stomach in Dogs

Dog No.	Operation	Preoperative Threshold, in Mm. Hg	Postoperative Threshold, in Mm. Hg
1	Transection of left vagus nerve in neck.....	47	54
2	Transection of left vagus nerve in neck.....	43	55
3	Transection of right vagus nerve in neck.....	63	45
2	Bilateral transection of vagus nerve in neck.....	43	45
23	Bilateral transection of vagus nerve in neck.....	60	50
132	Transection of right phrenic nerve in thorax.....	62	60
133	Transection of right phrenic nerve in thorax.....	55	60
133	Bilateral transection of phrenic nerve in thorax.....	55	55
68	Bilateral transection of phrenic nerve in neck.....	53	56
67	Bilateral transection of phrenic nerve in neck.....	50	48
72	Transection of left sympathetic trunk below splanchnic nerve..	58	60
73	Transection of left sympathetic trunk below splanchnic nerve..	60	56
108	Transection of left sympathetic trunk below splanchnic nerve..	40	38
112	Transection of left sympathetic trunk below splanchnic nerve..	50	58
128	Bilateral transection of sympathetic trunk below splanchnic nerve	55	60
72	Bilateral transection of sympathetic trunk below splanchnic nerve	58	55
129	Bilateral transection of sympathetic trunk below splanchnic nerve	55	58
134	Bilateral transection of sympathetic trunk below splanchnic nerve	55	58
33	Transection of spinal cord at C8 - T1.....	42	75
41	Transection of spinal cord at C8 - T1.....	40	No pain
42	Transection of spinal cord at T1 - T2.....	60	No pain
48	Transection of spinal cord at T2 - T3.....	45	90
45	Transection of spinal cord at T3 - T4.....	50	100
98	Transection of spinal cord at T3 - T4.....	55	120
49	Transection of spinal cord at T4 - T5.....	50	80
145	Transection of spinal cord at T4 - T5.....	55	80
159	Transection of spinal cord at T5 - T6.....	53	95
50	Transection of spinal cord at T5 - T6.....	50	55
146	Transection of spinal cord at T5 - T6.....	52	70
161	Transection of spinal cord at T5 - T6.....	60	60
75	Transection of spinal cord at T7 - T8.....	60	50
167	Transection of spinal cord at T7 - T8.....	55	55
166	Transection of spinal cord at T8 - T9.....	50	60
62	Transection of left splanchnic nerve.....	42	60
53	Transection of left splanchnic nerve.....	45	52
166	Transection of left splanchnic nerve.....	58	95
69	Transection of right splanchnic nerve.....	55	112
65	Transection of right splanchnic nerve.....	40	70
111	Transection of right splanchnic nerve.....	50	45
107	Transection of right splanchnic nerve.....	65	45
51	Transection of right splanchnic nerve.....	55	55
114	Transection of right splanchnic nerve.....	40	40
62	Bilateral transection of splanchnic nerve.....	52	83
69	Bilateral transection of splanchnic nerve.....	55	93
114	Bilateral transection of splanchnic nerve.....	50	50
107	Bilateral transection of splanchnic nerve.....	65	97
111	Bilateral transection of splanchnic nerve.....	50	92
156	Bilateral transection of splanchnic nerve.....	53	110
139	Transection of left rami communicantes, T8 through T13.....	60	72
160	Transection of left rami communicantes, T8 through T13.....	60	70
142	Transection of right rami communicantes, T7 through T13.....	50	85
138	Transection of right rami communicantes, T8 through T13.....	52	62
142	Bilateral transection of rami communicantes, T7 through T13	50	118
148	Bilateral transection of rami communicantes, T8 through T13	60	50
154	Bilateral transection of rami communicantes, T8 through T13	55	85
138	Bilateral transection of rami communicantes, T8 through T13	52	75
35	Transection of posterior roots, T5 through T9.....	60	67
83	Transection of posterior roots, T3 through T7.....	50	53
79	Transection of posterior roots, T4 through T7.....	40	50
89	Transection of posterior roots, T5 through T11.....	55	60
136	Transection of posterior roots, T5 through T13.....	50	78
133	Transection of posterior roots, T6 through T13.....	52	75
155	Transection of posterior roots, T8 through T12.....	55	100
155	Transection of posterior roots, T7 through T12.....	60	90
162	Transection of posterior roots, T6 through T11.....	55	90
89	Transection of posterior roots, T5 through L2.....	60	110
83	Transection of posterior roots, T3 through L3.....	52	105
136	Transection of posterior roots, T9 through T13.....	50	78
135	Transection of posterior roots, T10 through L4.....	55	72
135	Transection of posterior roots, L1 through L4.....	55	58
88	Transection of anterior roots, T3 through T6.....	50	40
96	Transection of anterior roots, T4 through T10.....	60	60
71	Transection of anterior roots, T5 through T11.....	60	58
94	Transection of anterior roots, T4 through T13.....	55	48
88	Transection of anterior roots, T3 through T13.....	50	58
94	Transection of anterior roots, T4 through L4.....	55	52
96	Transection of anterior roots, T4 through L4.....	60	52
130	Transection of anterior roots, T10 through L7.....	50	54
130	Transection of anterior roots, T3 through L7.....	50	50
121	Transection of anterior and posterior roots, T4 through T10.	55	55
122	Transection of anterior and posterior roots, T4 through T10.	45	50
122	Transection of anterior and posterior roots, T4 through L2..	45	115
127	Transection of anterior and posterior roots, T13 through L4..	60	58
152	Removal of left sympathetic trunk between 3d and 9th ribs....	45	90
144	Removal of left sympathetic trunk between 4th and 9th ribs....	55	55

*Results of Determination by Surgical Methods of Pathways for Pain from the
Stomach in Dogs—Continued*

Dog No.	Operation	Preoperative Threshold, in Mm. Hg	Postoperative Threshold, in Mm. Hg
141	Removal of right sympathetic trunk between 3d and 9th ribs...	55	62
152	Removal of left sympathetic trunk between 3d and 9th ribs and right sympathetic trunk between 4th and 9th ribs.....	45	70
144	Bilateral removal of sympathetic trunk between 4th and 9th ribs	55	56
153	Removal of left sympathetic trunk between 3d and 10 ribs and right sympathetic trunk between 2d and 9th ribs.....	45	45
113	Transection of left intercostal nerve, T4 through T11, just distal to posterior div.....	30	35
118	Transection of left intercostal nerve, T5 through T12, just distal to posterior div.....	55	62
119	Transection of right intercostal nerve, T5 through T12, just distal to posterior div.....	55	50
120	Transection of right intercostal nerve, T4 through T11, just distal to posterior div.....	45	48
123	Bilateral transection of intercostal nerve, T6 through T12, just distal to posterior div.....	55	53
126	Bilateral transection of intercostal nerve, T5 through T12, just distal to posterior div.....	60	55
124	Bilateral transection of intercostal nerve, T5 through T12, just distal to posterior div.....	60	63
158	Bilateral transection of posterior roots, T8 through T12.....	55	100
158	Bilateral transection of posterior roots, T8 through T12, transection of left sympathetic trunk below splanchnic nerve and at level of 6th rib.....	55	90
158	Bilateral transection of posterior roots, T8 through T12, + bilateral transection of sympathetic trunk below splanchnic nerve and at level of 6th rib.....	55	100
158	Bilateral transection of posterior roots, T8 through T12, — bilateral transection of sympathetic trunk below splanchnic nerve and at level of 6th rib + bilateral transection of greater splanchnic nerve.....	55	120

Unilateral transection of the left greater splanchnic nerve increased the thresholds for pain following distention of the stomach by an average pressure of 22 mm. of mercury, whereas unilateral transection of the right greater splanchnic nerve increased the thresholds for pain by an average of only 11 mm. of mercury (table). Bilateral transection of the greater splanchnic nerve in the same dogs, however, raised their thresholds for pain from an average preoperative level of 53 mm. to an average postoperative level of 93 mm. of mercury (table). These experiments indicate that the greater splanchnic nerve of the dog contains at least the greater majority of the afferent fibers which mediate pain following distention of the stomach. The left greater splanchnic nerve probably contains a greater number of these fibers than does the right.

Unilateral transections of the rami communicantes of the seventh or eighth through the thirteenth thoracic spinal nerve on the right side increased the thresholds for pain following distention of the stomach by an average pressure of 22 mm. of mercury, whereas the same operative procedure on the left side increased the thresholds for pain by an average pressure of only 11 mm. of mercury (table). We are unable to explain why these results are contrary to those of unilateral transection of the greater splanchnic nerve. Bilateral transection of these particular rami communicantes in the same dogs, however, raised the thresholds for pain from an average preoperative level of 52 mm. to an average postoperative level of 90 mm. of mercury (table). These results compare favorably with those obtained after bilateral transection of the greater splanchnic nerve.

Extensive bilateral transections of the posterior roots of the spinal nerves were performed on 3 dogs. In the first dog the posterior rhizotomies extended from the third thoracic through the third lumbar spinal nerves; those in the second dog, from the fourth thoracic through the fourth lumbar spinal nerves, and those in the third dog, from the fifth thoracic through the second lumbar spinal nerves (table). In each case the postoperative threshold for pain following distention of the stomach showed an increase of 50 mm. of mercury or more over the preoperative

level. A comprehensive series of experiments involving less extensive posterior rhizotomies were performed on 12 dogs (table). These experiments included posterior rhizotomies on the upper thoracic, the combined upper and middle thoracic, the middle thoracic, the combined middle and lower thoracic, the lower thoracic, the combined lower thoracic and upper lumbar and the upper lumbar nerves. It was found that the postoperative threshold for pain was elevated by at least 25 mm. of mercury provided that the posterior roots of the eighth through the thirteenth thoracic spinal nerve had been transected.

The spinal cords of 15 dogs were transected at different levels through the cervical and thoracic regions of the cord (table). The results of these experiments indicate that a chordotomy through any level of the spinal cord cephalic to its fourth thoracic segment will abolish completely the pain initiated by distention of the stomach. Transection of the spinal cord between its fourth and its seventh thoracic segment usually raised the threshold but seldom abolished completely the pain resulting from distention of the stomach. Chordotomy below the level of the seventh thoracic segment of the spinal cord had no effect on the threshold for pain following distention of the stomach.

The sympathetic trunk between the levels of the third or fourth and the ninth or tenth rib was removed unilaterally (table). Removal of the right sympathetic trunk, and in 1 of 2 cases removal of the left sympathetic trunk, did not affect the thresholds for pain following distention of the stomach. The second dog in which the left sympathetic trunk was removed showed, however, an increased threshold for pain amounting to a pressure of 45 mm. of mercury. Bilateral removal of these portions of the sympathetic trunk (table) provoked no change in the threshold for pain in 2 out of 3 dogs. The third dog, however, had a postoperative threshold for pain which was 25 mm. of mercury higher than its base line. In a few dogs the thickened portion of the sympathetic trunk, owing in all probability to the presence of afferent fibers from the greater splanchnic nerve, extends cephalad to the vicinity of the eighth rib. Should this portion of the sympathetic trunk be traumatized, one would expect an increase in the threshold for pain comparable to that resulting from damage to the greater splanchnic nerve.

Extensive bilateral transections of the anterior roots of the spinal nerves were performed in 3 dogs. In the first dog the anterior rhizotomies extended from the third thoracic through the seventh lumbar spinal nerve, whereas the operation in the second and third dogs extended from the fourth thoracic through the fourth lumbar spinal nerve (table). In no case was there any detectable difference in the preoperative and the postoperative threshold for pain.

Combined transections of the anterior and posterior roots of the thoracic and lumbar spinal nerves were performed in 4 dogs (table). In no instance did any of these animals show any change in their thresholds for pain other than what would be expected to follow transections of the posterior roots alone.

In 5 dogs, the lower seven intercostal nerves were transected unilaterally and bilaterally just distal to the point of origin of the posterior division of each nerve (table). These operative procedures appeared to have no effect on the thresholds for pain following distention of the stomach.

The following experiment was performed on 1 dog in an attempt to limit more closely the neurologic pathway which mediates pain from the stomach. Bilateral transections of the posterior roots of the eighth through the twelfth thoracic spinal nerve were performed. The threshold for pain, following this operative procedure, was increased by a pressure of 45 mm. of mercury. The threshold for pain continued at this level after bilateral transection of the sympathetic trunk at the level of the sixth rib and, again, just caudad to the origin of the greater splanchnic nerve.

After a bilateral transection of the greater splanchnic nerve, however, the threshold for pain increased by an additional pressure of 20 mm. of mercury. As has been stated elsewhere, it is necessary to transect the posterior roots of the fourth thoracic through the third lumbar spinal nerve in order to alleviate completely the pain which follows distention of the stomach in the dog. The results of the experiment just described would, therefore, indicate that the posterior roots of the sixth, seventh and thirteenth thoracic spinal nerves are capable of mediating a considerable portion of the pain resulting from distention of the stomach.

COMMENT

We believe that the peculiar steplike type of expiration which was observed in all dogs after distention of the stomach is an objective sign of the pain experienced by the animal. The presence of this sign following distention of the stomachs of dogs in which bilateral transections of the phrenic and vagus nerves and of the anterior roots of the thoracic and lumbar spinal nerves had been performed indicates that this sign is not dependent for its appearance on the phrenic nerve, the vagus nerve or the anterior roots of the thoracic and lumbar spinal nerves. It would appear, therefore, that this sign is not initiated by stress or embarrassment of the mechanism for respiration. When the spinal cord is transected cephalad to the fourth thoracic segment, the peculiar steplike type of expiration does not appear, except at intragastric pressures above approximately 105 mm. of mercury. This fact indicates that the sign is not the result of a spinal cord reflex and that it does depend for its appearance on higher centers in the central nervous system.

No significant changes in the thresholds for pain could be observed after repeated distentions of the stomach of the same dog over intervals as long as seven months. These observations indicate that adaptation of the stomach, under the conditions of this investigation, does not occur and bears no relationship to any increased postoperative threshold for pain. Gastric fistulas were constructed in one group of dogs, so that the stomach could be distended by an air-filled balloon in the absence of any anesthetic. The preoperative threshold for pain which was recorded while the dog was under very light ether anesthesia was identical with the postoperative threshold for pain recorded in the absence of any anesthetic. It is believed, therefore, that the state of anesthesia employed in this investigation does not alter materially the thresholds for pain following distention of the stomach. No change in the thresholds for pain was evident after ligation of the arteries and veins of the stomach. These results suggest that the threshold for pain following distention of the stomach is not affected by either venous or arterial congestion of that organ.

It is believed that the appearance of the peculiar steplike type of expiration following intragastric pressures at or above 105 mm. of mercury is due to pain which originates in the body wall and/or the structures and organs adjacent to the stomach. This is indicated by the results of an experiment in which the peritoneal cavities of 5 dogs were distended with air by means of a hypodermic needle inserted through an anesthetized area of the abdominal wall. The peculiar steplike type of expiration appeared in each case when the intra-abdominal pressure became elevated to between 105 and 110 mm. of mercury. It is believed, therefore, that the pain which follows intragastric pressures up to approximately 105 mm. of mercury originates in the stomach and its mesenteries.

Transection of the nerves containing the afferent fibers from the stomach should therefore raise the threshold for pain to a pressure of approximately 105 mm. of mercury, and it was by this means that the sensory pathway was traced. It should be pointed out, however, that the surgical method for tracing sensory pathways

is not adapted for estimating quantitatively the number of fibers mediating pain in any one nerve. It is distinctly possible that some nerve trunk might contain a few of the fibers mediating pain from an organ which, when all the remaining fibers of the pathway were intact, would conduct actually a relatively low percentage of the total number of the impulses initiated by the stimulation of the organ. If, on the other hand, these aberrant fibers were the only fibers of the pathway remaining intact, it is quite possible that they might deliver to the higher centers impulses in sufficient number to bring about the sensation of pain at the same threshold as it would have been produced had the entire pathway been intact. The investigations of Dusser de Barenne⁴² indicate that under certain conditions neurologic mechanisms of this type do exist.

The results of the experiments already described indicate that in dogs the pain which accompanies distention of the stomach is mediated by afferent fibers which traverse the greater splanchnic nerve to the sympathetic trunk. The majority of these fibers probably enter the spinal cord via the rami communicantes and the corresponding posterior roots of the eighth through the thirteenth thoracic spinal nerve. This is indicated by the fact that transections of the rami communicantes or of the posterior roots of these nerves result in an elevation of the threshold for pain amounting to 25 mm. or more of mercury.

It has been noted that a more extensive posterior rhizotomy (extending from at least the fourth through the third lumbar spinal nerve) had to be performed in order to produce a maximal elevation of the threshold for pain after distention of the stomach (which was a pressure of approximately 105 mm. of mercury). This fact indicates that certain of the fibers which mediate pain from the stomach of the dog ascend and descend within the sympathetic trunk as far cephalad as the fourth thoracic and as far caudad as the third lumbar sympathetic ganglia. These ascending and descending fibers undoubtedly enter the spinal cord via the rami communicantes and the posterior roots of the fourth through the seventh thoracic and the first through the third lumbar spinal nerve. That these ascending and descending fibers are probably not of major physiologic importance when the rami communicantes and the posterior roots of the eighth through the thirteenth thoracic spinal nerve are intact is shown by the results of 3 experiments. In the first experiment, the sympathetic trunk was transected bilaterally just caudad to the origin of the greater splanchnic nerve from the sympathetic trunk; in the second experiment, the sympathetic trunk was transected bilaterally at the level of the sixth rib and again just caudad to the origin of the greater splanchnic nerve from the sympathetic trunk; in the third experiment, the sympathetic trunk was removed bilaterally between the levels of the third and the eighth or ninth rib. Elevation of the postoperative threshold for pain following distention of the stomach occurred in only 2 dogs of this group. We believe that these exceptions can be explained on the basis that in some dogs the thickened portion of the sympathetic trunk, undoubtedly caused by the presence of afferent fibers from the greater splanchnic nerve, extends cephalad to the vicinity of the eighth rib. Therefore, it is obvious that trauma to the thickened portion of the sympathetic trunk would produce changes in the threshold for pain similar to that following damage to, but not complete interruption of, the greater splanchnic nerve.

It was shown that the pain which follows dilatation of the stomach is obliterated by transection of the spinal cord at any level above its fourth thoracic segment. Successive transections of the spinal cord between its fourth and its seventh thoracic segment result in progressive lessening of the differences between the

42. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, *A. Research Nerv. & Ment. Dis.*, Proc. 15:274, 1935.

preoperative and the postoperative threshold for pain. Transection of the spinal cord below the level of its seventh thoracic segment has no effect on the threshold for pain following distention of the stomach. This gradual diminution of the difference between the preoperative and the postoperative threshold for pain is due apparently to a progressive increase in the number of afferent fibers entering the spinal cord from the stomach as one progresses from the upper through the middle region of the thoracic portion of the spinal cord.

It is obvious from these observations that the results which were obtained after transection of the spinal cord are not in agreement with those obtained after transections of the posterior roots or of the rami communicantes of the eighth through the thirteenth thoracic spinal nerve. It has been stated elsewhere that transection of the posterior roots or of the rami communicantes of the eighth through the thirteenth thoracic spinal nerve is followed by an increase in the threshold for pain amounting to a pressure of 25 mm. or more of mercury. On the other hand, transection of the spinal cord caudad to the level of its seventh thoracic segment, an operative procedure which should interrupt any sensory pathway traversing the posterior roots or the rami communicantes of the eighth through the thirteenth thoracic spinal nerve, has no effect on the threshold for pain after distention of the stomach. Since the results of the various experiments already reported in this paper have indicated that thirteen posterior roots (fourth thoracic to third lumbar inclusive) contain sensory fibers mediating pain from the stomach, it is of interest to note that transection of the spinal cord caudad to its seventh thoracic segment fails to alter the threshold for pain, although only three of the original thirteen posterior roots, the fourth through the seventh thoracic, remain intact. Since transection of these posterior roots only is not associated with elevation of the threshold for pain, it is possible that certain peculiar circumstances may be attendant on a chordotomy which is performed immediately caudad to the seventh thoracic segment.

It is conceivable that these circumstances might lower the threshold for pain, by some mechanism local to the spinal cord, to such a degree that painful impulses, entering the spinal cord through the posterior roots of the fourth through the seventh thoracic spinal nerve, could reach the higher centers in sufficient numbers and strength to produce the sensation of pain when the stomach is distended to the level of its preoperative threshold for pain. We are unaware of any evidence in the literature or in the present studies which would prove this hypothesis, although the same general type of mechanism has been demonstrated by Dusser de Barenne.⁴² This investigator showed that strychninization of a small portion of the posterior surface of one half of a segment of the spinal cord is followed by hyperesthesia in the entire dermatome supplied by the corresponding root. Furthermore, acute inflammatory states of the spinal cord, as might conceivably exist after chordotomy, are generally recognized as producing hyperalgesic states.

The weight of evidence shown by this investigation indicates that the afferent fibers which mediate the pain caused by distention of the stomach traverse the greater splanchnic nerve to the sympathetic trunk. These conclusions are in accord with the observations of Kappis,¹⁵ Lebendenko and Brjussowa,¹⁰ Duschl,²⁷ Cannon²⁸ and Alvarez.² From the sympathetic trunk it would appear that the afferent fibers enter the spinal cord over one main and two subsidiary routes. The main route is via the rami communicantes and the posterior roots of the eighth through the thirteenth thoracic spinal nerve. Of the two subsidiary routes, the first, comprising the rami communicantes and the posterior roots of the fourth through the seventh thoracic spinal nerve, is probably of greater physiologic importance than is the second, consisting of the rami communicantes and the

posterior roots of the first through the third lumbar spinal nerve. Our observations relative to the entrance into the spinal cord of the sensory fibers from the greater splanchnic nerve are not in agreement with the conclusions of Ross³⁰ and of Ranson and Billingsley.³¹

Experiments carried out during this study have shown that neither the phrenic nor the vagus nerve is concerned with mediation of the pain which results from dilatation of the stomach in the dog. This conclusion agrees with the observation of Langley,²³ Kappis,²⁵ Breslauer,⁸ Lebendenko and Brjussowa,¹⁰ Duschl,²⁷ Alvarez²⁰ and Cannon.²⁸

Davis and Pollock⁴³ stated that bilateral transection of the intercostal nerves relieved some of the pain which resulted from experimental distention of the gallbladder. They concluded from this observation that referred pain was probably present. In contrast to their observation, it has been shown in the present study that bilateral transection of the lower seven intercostal nerves in the dog did not change the threshold for the pain which follows distention of the stomach. It is our conclusion, therefore, that pain referred to the sensory terminals of somatic peripheral nerves does not exist in the dog after distention of the stomach. The absence of this type of pain seems even more likely since in no instance was it possible to discern areas of cutaneous hyperalgesia or of hypertonicity of somatic musculature after distention of the stomach. Furthermore, we were unable to elevate the threshold or abolish the pain following distention of the stomach by infiltrating the skin over the back and abdomen with procaine hydrochloride.

Weiss and Davis⁴⁴ expressed the belief that the intercostal nerves are of importance in the mediation of referred pain initiated by noxious stimulation of the viscera. These investigators studied the cutaneous areas to which pain was referred in 25 patients suffering from visceral disease; in addition, they studied normal persons in whom the esophagus and duodenum were distended with air-filled balloons. They reported that the sites of cutaneous pain could be abolished by infiltrating the skin with procaine and that unless the original sites of cutaneous pain were localized distinctly, the painful areas tended to shift to neighboring regions when the original sites were anesthetized. The experiments reported in the present paper offer no evidence in support of this conception.

According to Spameni and Lunedei⁴⁵ afferent fibers from the viscera enter the spinal cord and terminate on centrifugal neurons, which leave the spinal cord by way of the anterior roots and terminate in the sensory corpuscles within the skin. Impulses carried to the sensory corpuscles by these centrifugal neurons are thought to excite neighboring somatic afferent fibers, which, in turn, convey impulses to conscious levels, where they are interpreted as pain originating in the skin. Verger⁴⁶ stated that afferent impulses from a stimulated viscus enter the spinal cord and terminate on certain sympathetic neurons, which were said to leave the spinal cord by way of the posterior roots and to terminate on the "cutaneous vascular bouquets." Excitation of these particular sympathetic neurons supposedly modified the vascular bouquets in such a manner as to stimulate neighboring somatic

43. Davis, L., and Pollock, L. J.: Visceral Pain, *Surg., Gynec. & Obst.* **55**:418, 1932.

44. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin in the Mechanism of Pain: Skin Infiltration as a Useful Therapeutic Measure, *Am. J. M. Sc.* **176**:517, 1928.

45. Spameni, P., and Lunedei, A.: Sui riflessi viscerocutanei e sul meccanismo di produzione del dolore nelle affezioni dei visceri e delle sierose, *Riv. di clin. med.* **28**:758, 1927; cited by Pollock and Davis.³⁸

46. Verger, H.: Sur une modification due schème de Lemair pour la conception physiologique de réflexe viscéro-sensitif de Mackenzie, *Gaz. hebdomadaire de médecine de Bordeaux* **43**:419, 1927; cited by Pollack and Davis.³⁸

afferent neurons. These fibers, in turn, conveyed impulses to conscious levels which were interpreted as pain which had arisen within the skin. Wernøe⁴⁷ reported that a wide variety of viscerocutaneous reflexes can be observed after stimulation of various parts of the gastrointestinal tract. The experiments reported in the present paper offer no evidence in support of the ideas presented by these workers.

SUMMARY AND CONCLUSIONS

In this study an effort was made to outline the neurologic pathway for mediation of the pain which follows distention of the stomach in the dog. One hundred and fifty-eight dogs of 10 to 15 pounds (4.5 to 6.8 Kg.) in weight were employed.

Pain was produced by distending the stomach with an air-filled balloon. A method for graphically recording a constant response to the painful stimulus is described. This objective sign of pain, a peculiar steplike type of expiration, was shown to be independent of the vagus and phrenic nerves and of the anterior roots of the thoracic and lumbar spinal nerves. It was concluded from these observations that the sign is not initiated by stress or embarrassment of the mechanism for respiration. Evidence was presented that the sign was not dependent for its appearance on venous or arterial congestion of the stomach and that it did not involve a spinal cord reflex.

It was found that the respiratory index for pain in the dog on which no operation had been performed was evident when the intragastric pressure was elevated to 50 to 60 mm. of mercury. The threshold for this response remained constant for each animal which had not been operated on and did not change significantly after repeated inflations of the stomach for periods as long as seven months.

The results of this investigation indicate that visceral afferent nerve fibers only are involved in the mediation of the pain which follows distention of the stomach in the dog and that they are contained within the greater splanchnic nerve. The majority of these fibers traverse the rami communicantes of the eighth through the thirteenth thoracic spinal nerve and enter the spinal cord through the corresponding posterior roots. Evidence was presented which indicates that some of these fibers traverse the sympathetic trunk as far cephalad as the fourth thoracic and as far caudad as the third lumbar sympathetic ganglion. These particular fibers undoubtedly enter the spinal cord over the rami communicantes and the corresponding posterior roots of the fourth through the seventh thoracic and the first through the third lumbar spinal nerve.

We were unable to elevate the threshold or abolish the pain following distention of the stomach by infiltrating the skin over the back and abdomen with procaine or by performing bilateral transections of the lower seven intercostal nerves and of the anterior roots of the thoracic and lumbar spinal nerves. In no case were we able to discern areas of cutaneous hyperalgesia or of hypertonicity of somatic musculature following distention of the stomach. It is our conclusion, therefore, that pain referred to the sensory terminals of somatic peripheral nerves does not exist in the dog after distention of the stomach.

Wayne University College of Medicine.

⁴⁷ Wernøe, T. B.: Viscero-cutane Reflexe, *Arch. f. d. ges. Physiol.* **210**:1, 1925.

FORMATION OF DEMYELINATED PLAQUES ASSOCIATED WITH CEREBRAL FAT EMBOLISM IN MAN

I. MARK SCHEINKER, M.D.

CINCINNATI

This presentation is concerned with a detailed histopathologic study of the cerebral lesions associated with fat embolism. Their analysis revealed certain similarities to the early focal lesions of demyelination occurring in cases of disseminated sclerosis.

REPORT OF CASES

CASE 1.—History.—A 20 year old white man, a student, had been struck by an automobile one hour before admission to the hospital. Roentgen studies revealed comminuted fracture of the middle third of the left tibia and fibula. The previous history was normal.

On the morning of admission (1 a. m.) the patient was alert, and the results of physical examination were normal except for fracture of the left leg. He failed to respond during early morning care, and an hour later he could not be aroused for breakfast. He never regained consciousness. Urinary and fecal incontinence was noted. The temperature was 101.6 F., the pulse rate 100, the respiratory rate 26 and the blood pressure 114 systolic and 90 diastolic. Supraorbital pressure failed to arouse him. The pupils were moderately contracted and responded slightly to light. There was spontaneous nystagmus. Examination of the eyegrounds revealed no abnormality. Both upper extremities were spastic, the left more so than the right. The achilles and patellar reflexes were more active on the right, and there was a Babinski response on that side.

On the third day in the hospital a diffuse, petechial hemorrhagic rash developed in the skin over the axillas, chest, abdomen, flanks and groins. Cheyne-Stokes breathing was observed. The patient died on the fifth day.

General Autopsy.—The skin of the entire body presented an enormous number of minute, punctate hemorrhagic lesions. Lesions of similar appearance were seen in the heart muscle, peritoneum, liver, spleen and kidneys. Gentle pressure on the cut surface of the lung caused a few small fat droplets to exude. Microscopic sections of the skin and of all the viscera prepared by the special technic with osmic acid and sudan III showed capillaries plugged with fat droplets. The accumulations of fat were most abundant in the lung.

Gross Examination of Brain.—Throughout the gross sections of the brain there were observed multiple pink points, ranging from the size of a pinpoint to 2 mm. in diameter. They were scattered throughout the white and the gray matter indiscriminately, though they were more prominent in the white (fig. 1). Inferiorly both caudate nuclei were softened; the area of this gross change measured 6 to 8 mm. in diameter. In the medial extent of the right caudate nucleus there was a hemorrhagic area, measuring 3 mm. in diameter. There were marked congestion of the blood vessels and some perivascular hemorrhage.

Microscopic Study of Brain.—Sections from several cortical areas, the midbrain, the medulla and the cerebellum were stained with hematoxylin and eosin and cresyl violet and by the Loyez myelin sheath, the Bodian 1 per cent protargol (strong protein silver) and the scarlet red method.

Histologic examination revealed two types of abnormalities, which were sometimes combined and sometimes observed separately. An interesting manifestation was the presence of circumscribed, diffusely disseminated patches of demyelination, throughout the brain substance, most prominent in the subcortical areas. Analysis of the histologic structure of these lesions revealed two distinct types: (a) Circumscribed areas of focal necrosis characterized by complete cellular destruction, loss of myelin sheaths and nerve fibrils and rarefaction of the tissue. These areas of degeneration contained no cellular elements except a few histiocytes. There were no fat granule cells and no inflammatory reaction. The majority of these foci suggested a perivascular distribution. Usually they contained a central capillary plugged with

From the Laboratory of Neuropathology, Cincinnati General Hospital, and the University of Cincinnati College of Medicine.

fat droplets (fig. 2). These lesions may be classified as an acute form of necrosis resulting from sudden interruption of the blood supply by the fat embolus. (b) Lesions characterized by destruction of myelin sheaths (figs. 3 and 4), partial preservation of axis-cylinders (fig. 5) and an early stage of repair, consisting of glial cell proliferation (fig. 7).

Axonal changes are illustrated in figures 5 and 6. The neurofibrils were swollen and thickened, with irregular beading, and intensely stained. In the central part of the patch, which contained the more extensively deteriorated tissue, the nerve fibrils revealed more advanced lesions in the form of fragmentation and poor impregnation (fig. 5). Some nerve fibers were broken into granular debris or were undergoing vacuolation. This advanced altera-

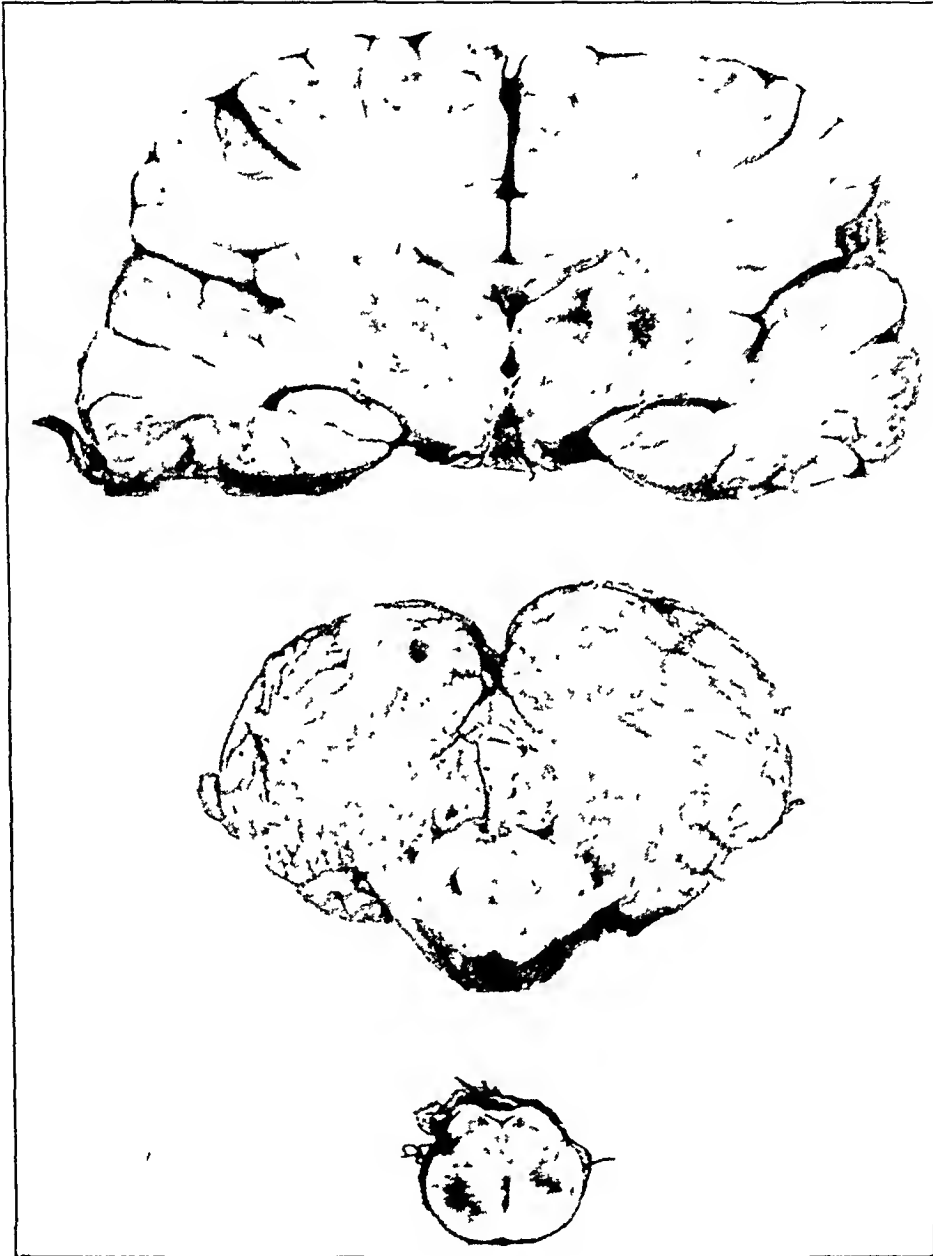


Fig. 1 (case 1).—Petechial hemorrhages scattered throughout the white and gray matter.

tion of the nerve fiber was observed only occasionally. As a rule the axis-cylinders were preserved and showed a relative increase in size of either isolated axons or groups of axons unassociated with any other obvious change. The swollen fibers in transverse section appeared circular, granular or homogeneous (fig. 6); the outline of the large fibers was often irregular.

Loyez and Spielmeyer myelin sheath preparations revealed complete disappearance or extensive degeneration of myelin in the majority of the patches (figs. 3 and 4). Occasionally a small number of myelin sheaths were preserved; they were irregular in outline and frequently were broken up into globules. These areas of demyelination resembled the lesions in cases of multiple sclerosis which Spielmeyer described as shadow patches (*Markschatteherde*).

A striking manifestation of the process was the presence of early stages of glial repair in some of the areas of demyelination. The cell stain revealed the presence of compact accumulations of glia cells. These cells usually varied considerably in size and shape (fig. 7). With the Cajal gold chloride-mercury bichloride stain the majority showed the characteristic structure of glia cells. There was a slight accumulation of microglia about the margin of some of the patches of demyelination. The nerve cells in some of the areas of demyelination were well preserved (fig. 7). A slight perivascular accumulation of round cells was present occasionally in the tissue surrounding the patches.

The changes in the cerebral capillaries and their relationship to the disseminated focal lesions deserve special attention. Specific stains (scarlet red) revealed numerous fat emboli



Fig. 2 (case 1).—Demyelinated plaque, with a central capillary plugged with a fat embolus. Spielmeyer myelin sheath stain; $\times 100$.

in the majority of the capillaries situated in or about the patches of demyelination. Only occasionally were the latter avascular. It is likely that an associated blood vessel would have been found in each if serial sections had been made.

What appeared to be small punctate hemorrhages to the naked eye were recognized as conglomerations of numerous ring hemorrhages with low power magnification. They presented a clear, pale-stained center surrounded by a large ring of extravasated blood. The center usually contained a capillary plugged with fat (scarlet red) and surrounded by an area of necrotic tissue. These hemorrhages were probably due to obstruction of the lumens of the blood vessels by fat emboli; in other words, they were hemorrhagic infarcts.

CASE 2.—*History*.—A white man aged 62 was admitted to the hospital unconscious a few hours after he had been struck by an automobile. He had suffered compound fractures of the right tibia, the pelvis and the fourth and fifth fingers of the right hand. On the day of admission reduction and closure of the compound fractures of the tibia and amputation of the fifth finger were performed. After operation the patient was deeply cyanotic and gasping for breath. The respiratory rate hovered between 56 and 60 per minute. Roentgen ray examination of the chest revealed elevation of the diaphragm on the left and evidence of bronchopneumonia on the right. In spite of oxygen therapy the cyanosis persisted. The



Fig. 3 (case 1).—Perivascular area of demyelination with partly preserved myelin sheaths ("myelin shadow" plaque). Spielmeyer myelin sheath stain; $\times 100$.

patient died forty-eight hours after admission. Clinically, the diagnosis of pulmonary or cerebral fat embolism was considered.

General Autopsy.—Autopsy revealed a comminuted fracture of the lower third of the right tibia and compound fractures of the fourth and fifth fingers of the right hand. There were partial collapse and acute passive congestion of the lungs.

Gross Study of Brain.—The majority of the coronal sections of the brain revealed disseminated lesions similar to those described in case 1. In many of the sections there was pronounced congestion of the vessels, which were frequently surrounded by small peri-

vascular hemorrhages. The rostral sections of the brain stem and cerebellum contained diffusely scattered, pinpoint, pinkish spots of discoloration.

Microscopic Study of Brain.—Sections from the frontal, parietal, temporal and occipital lobes of both hemispheres and from the basal ganglia, the brain stem and the cerebellum were stained with hematoxylin and eosin and cresyl violet and by the Loyez, Spielmeyer, Bodian and scarlet red methods. Microscopic examination revealed disseminated areas of demyelination and the presence of small hemorrhages similar to those described in case 1. A detailed description will therefore be omitted, though, again, attention should be drawn to their similarity to focal lesions observed in cases of acute multiple sclerosis.

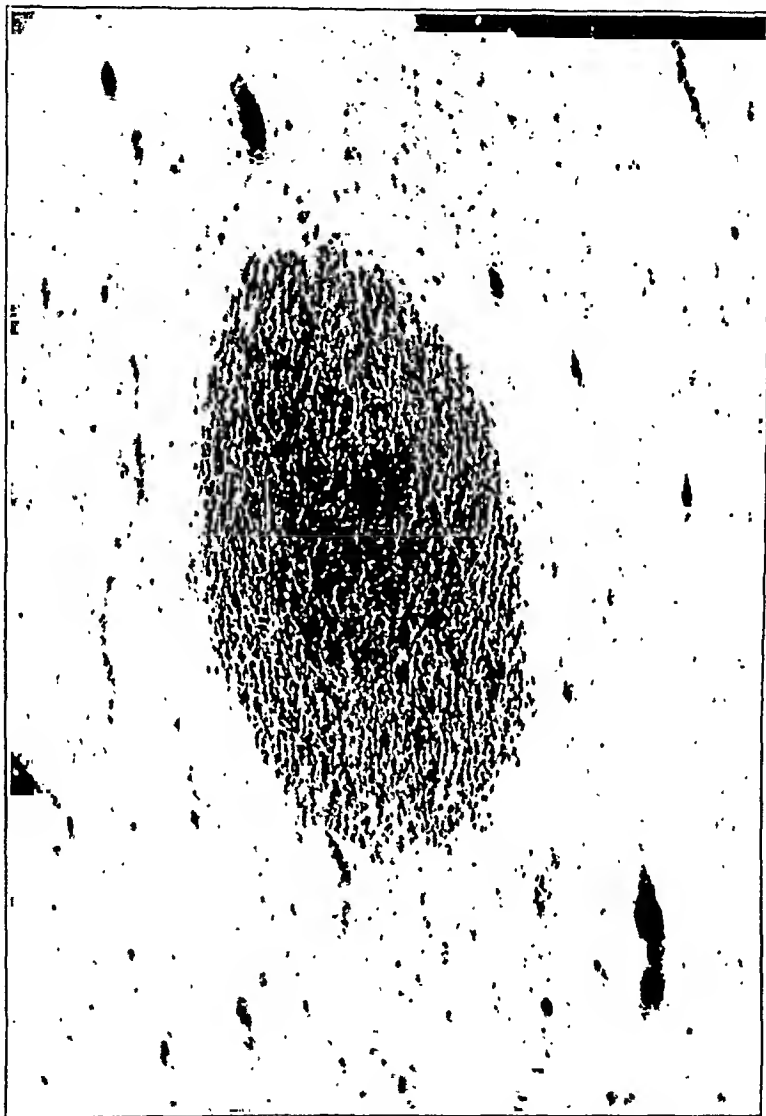


Fig. 4 (case 1).—Demyelinated plaque with preservation of numerous beaded and thinned myelin sheaths. Spielmeyer myelin sheath stain; $\times 100$.

Myelin sheath preparations revealed diffusely scattered, circumscribed areas of focal demyelination throughout the brain substance, most prominent in subcortical areas. They usually contained no cellular elements except for a few glial nuclei. The majority of the patches of demyelination appeared to be perivascular (fig. 8). They showed a central capillary completely occluded by fat globules. These circumscribed lesions appeared to be of different ages, the myelin being completely removed in some sections while in others swollen and fragmented myelin sheaths were still present. Bodian protargol preparations revealed partial preservation of the neurofibrils, although to a lesser degree than in case 1. Many of the remaining fibrils appeared swollen. Some of the lesions were devoid of cellular elements, representing complete degeneration and necrosis of all nerve elements. Here the tissue was

meshlike, and there was no proliferation of glia or capillaries. The latter lesions had all the characteristics of miliary, anemic infarcts.

Sections stained with scarlet red demonstrated the presence of fatty emboli in the capillaries and small veins. These oval globules sometimes occupied the entire lumen of the vessel. The fat emboli were most numerous within the areas of demyelination.

In addition to the disseminated patches of demyelination, the cerebral tissue showed two types of diffusely scattered punctate hemorrhages, the so-called ring hemorrhage and the perivascular hemorrhage. The ring hemorrhage usually consisted of a central capillary plugged with fat and surrounded by a small area of degenerated tissue, around which there was a

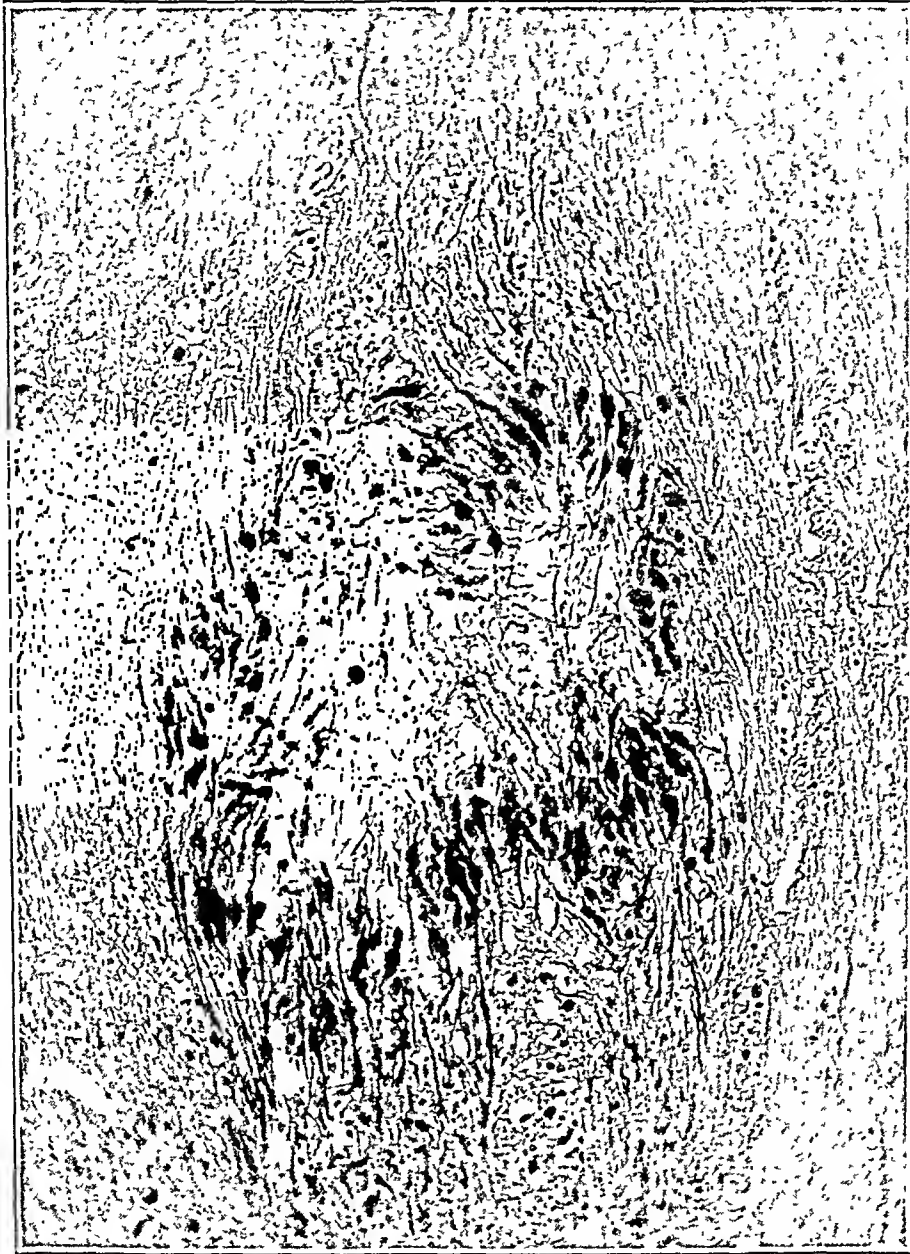


Fig. 5 (case 1).—Irregular swelling of axis-cylinders at the periphery of a plaque, with poor impregnation and fragmentation of the nerve fibrils in the center of the lesion. Bodian silver impregnation; $\times 122$.

large ring of red blood cells (fig. 9). The second type, the so-called perivascular hemorrhage, consisted of small arterioles and capillaries engorged with blood and surrounded by large masses of red blood cells limited to the distended perivascular spaces, some of which had been so distended that rupture and extravasation of red blood cells into the surrounding brain parenchyma had occurred. There was no indication of inflammatory reaction. The vessel walls exhibited no structural change.

Summary of Pathologic Changes.—It appears that the most constant and uniform pathologic change in the brain associated with fat embolism consists of

scattered, circumscribed areas of demyelination and necrosis. The focal areas of degeneration were of different ages and different structure.

Three types of focal lesions have been described: (1) Circumscribed areas of necrosis characterized by complete cellular destruction and loss of myelin sheaths and nerve fibrils, associated with rarefaction of the tissue. These areas usually contained a central capillary completely occluded by a fat embolus. (2) Lesions characterized by partial preservation of the nerve parenchyma and early signs of

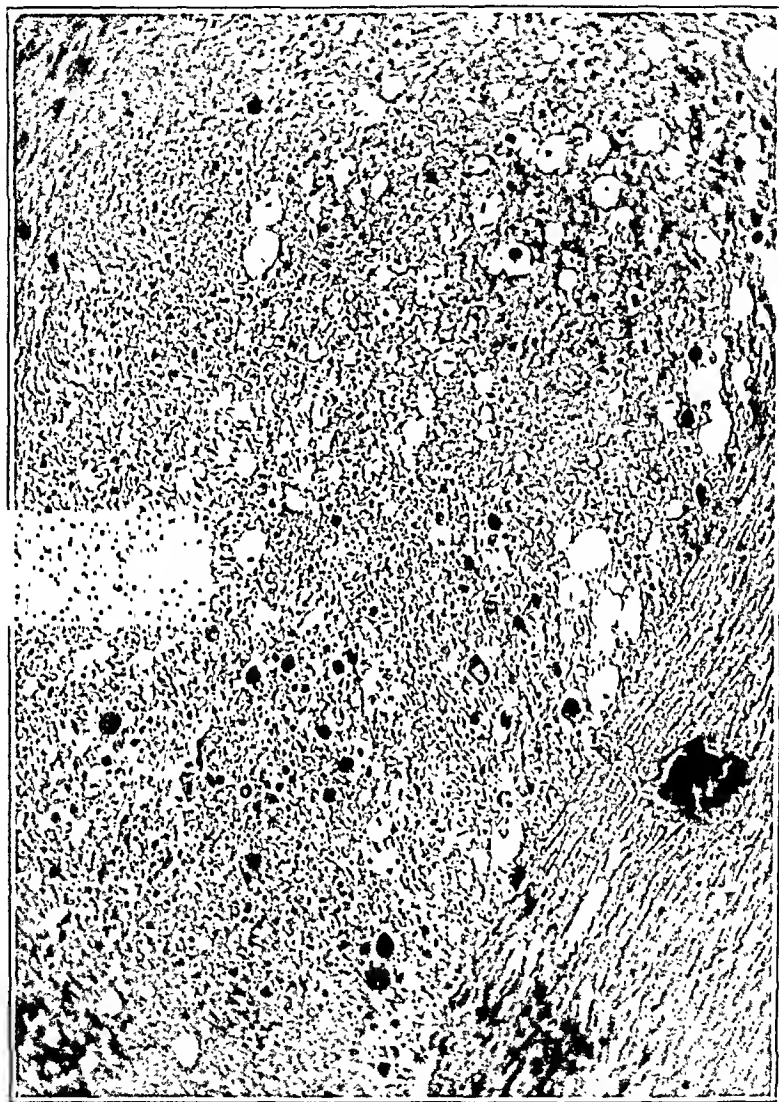


Fig. 6 (case 1).—Enormously swollen axis-cylinders in transverse section. Bodian silver impregnation; $\times 122$.

glial repair. These areas were similar to the early lesions of multiple sclerosis.¹ (3) So-called ring hemorrhages, consisting of a central capillary plugged with fat and surrounded by an area of necrotic tissue and a large ring of red blood cells. The last lesion is among the most common changes associated with cerebral fat embolism and may be considered as a minute hemorrhagic infarct.

1. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis: I. Significance of Vascular Changes, *Arch. Neurol. & Psychiat.* **49**:178-185 (Feb.) 1943.

COMMENT

The three types of focal lesions have in common alteration of the blood supply by the embolic occlusion of the capillaries. Their differences might be explained by variation in the rapidity and completeness of the occlusion, by the nature and size of the occluded blood vessel and by the "local factor" (Spielmeyer). It seems proper to assume that the degree of tissue damage may be dependent on the degree of focal cerebral hypoxia resulting from the circulatory disturbance. Whereas

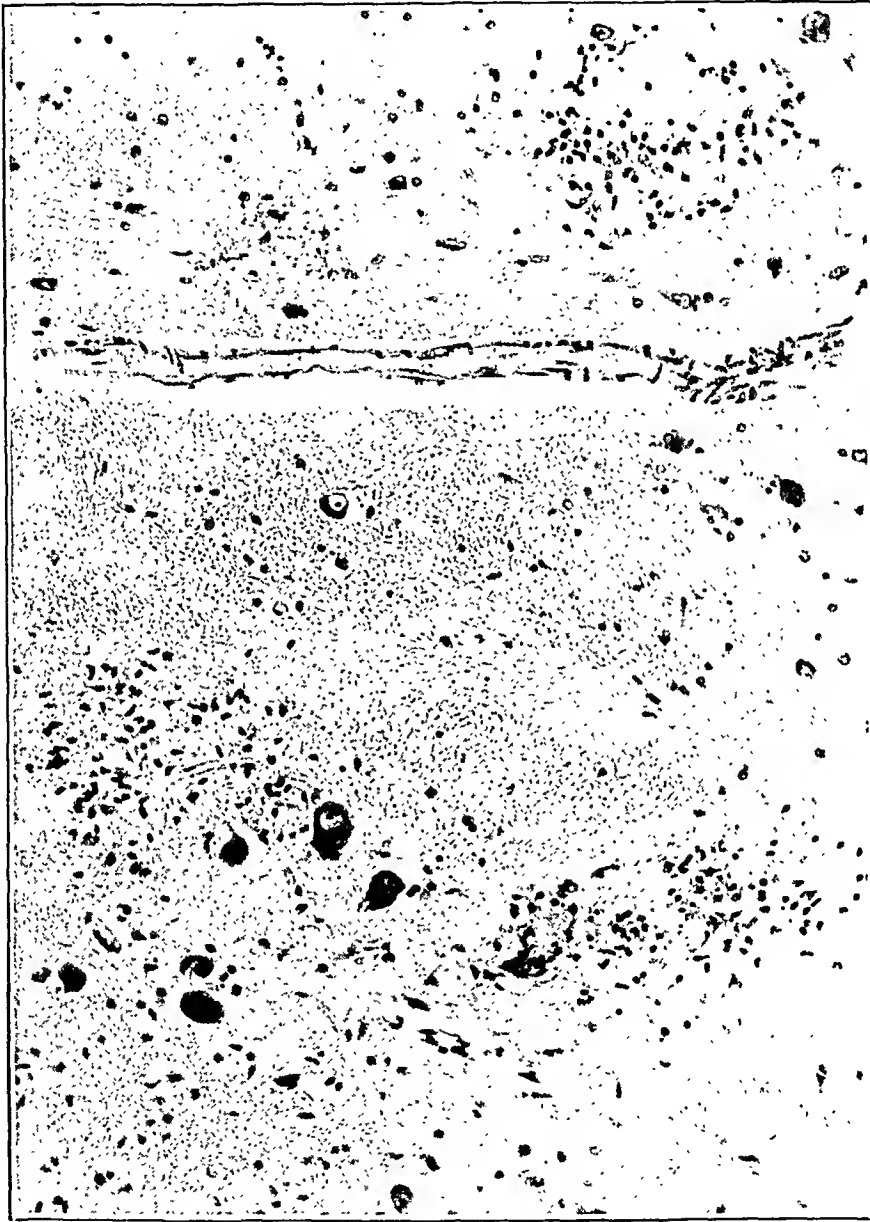


Fig. 7 (case 1).—Beginning of glial repair in the form of proliferation of glia cells. Note the preservation of cells of the basal ganglia. Cresyl violet; $\times 100$.

the devastating lesions might be interpreted as acute tissue destruction due to a sudden and complete interruption of the blood supply by the fat embolus, lesions of lesser severity may be due to slower development of, or less complete, circulatory embarrassment. Whereas with severe hypoxia the glia perishes together with the nerve parenchyma, in milder states of hypoxia there occurs relatively mild destruction of tissue limited particularly to the myelin sheaths. The nerve parenchyma and the supportive glia are partly preserved. The glia, though affected, is capable of proliferation, producing changes similar to those of the "early" lesions of dis-

seminated sclerosis.¹ If the morbid process were prolonged by survival of the patient, the glial proliferation probably would be replaced by proliferation of glial fibrils, and a true "sclerosis" would result.

Relatively few areas of tissue destruction were present in the cortex, though it contained many areas in which fat emboli were present. Probably the capillary anastomoses are so extensive that the nutrition of the tissue was only slightly impaired, if at all. In the white matter, where the capillary network is not so

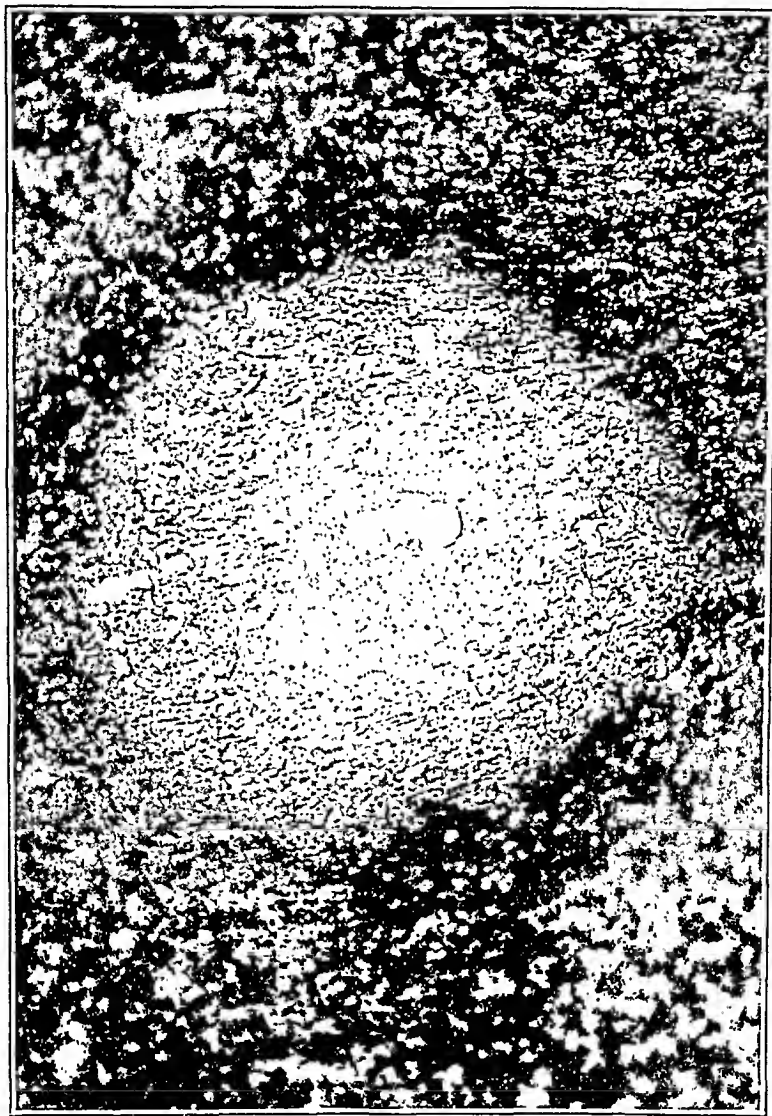


Fig. 8 (case 2).—Perivascular patches of demyelination with central capillaries. Spielmeier myelin sheath stain; $\times 100$.

extensive, the tissue damage was more severe and the number of necrotic areas more numerous.

Considerable difference of opinion exists as to the origin of ring hemorrhages. Frauentorfer² attributed the hemorrhage to rhexis of the blood vessel wall because of pressure from the embolus. Vance³ and Winkelman⁴ expressed the opinion that the ring hemorrhage represented a microscopic hemorrhagic infarct.

2. Frauentorfer, O.: Ueber Fettembolie, Beitr. z. gerichtl. Med. 6:1, 1924.

It is surprising that in spite of the existence of a voluminous literature dealing with fat embolism (there are over five hundred references at present) the changes in the nervous system seldom have been described in detail. An adequate review of the literature on fat embolism has been made by Winkelman.⁴ In his own cases Winkelman described the presence of two types of lesions, the ring hemorrhage and the small areas of necrosis termed "rarefied areas." He noted in some areas of necrosis "repair by gliosis and vascularization." His figure 8 illustrates



Fig. 9 (case 2).—Ring hemorrhages with central capillaries. Hematoxylin and eosin stain; $\times 100$.

beautifully beginning sclerosis around an occluded blood vessel. Vance,³ in his description of the early stage of the necrotic areas, mentioned the "preservation of the axis cylinders Later the process of repair sets in and glial cells tend to fill in the spaces."

3. Vance, B. M.: The Significance of Fat Embolism, *Arch. Surg.* **23**:426-465 (Sept.) 1931.

4. Winkelman, N.: Cerebral Fat Embolism, *Arch. Neurol. & Psychiat.* **47**:57-76 (Jan.) 1942.

SUMMARY

In a clinical and pathologic consideration of cerebral fat embolism, emphasis is placed on the diffusely scattered patches of demyelination, which are considered to be a constant and striking histopathologic feature of the disease.

The lesions of cerebral fat embolism are of two varieties: (*a*) miliary anemic infarcts, which result in focal areas of necrosis (destruction of all tissue elements), and (*b*) focal areas of demyelination with partial preservation of the nerve parenchyma (nerve cells and nerve fibrils) and early signs of glial repair.

The lesions of cerebral fat embolism are considered to be similar to the early lesions of multiple sclerosis.

Cincinnati General Hospital.

OCCLUSION OF THE ANTERIOR INFERIOR CEREBELLAR ARTERY

RAYMOND D. ADAMS, M.D.
BOSTON

The clinical picture which follows occlusion of the anterior inferior cerebellar artery is probably the least known of any of the cerebellar artery syndromes. To my knowledge only 1 such case has been reported, that of Goodhart and Davison.¹ Therefore, it seems worth while to record permanently the following case because of the clarity of the symptoms and the precise anatomic localization of the lesion.

ANTERIOR INFERIOR CEREBELLAR ARTERY (MIDDLE CEREBELLAR ARTERY)

This is probably the most variable of the cerebellar arteries. It usually originates as a branch of the basilar artery about 1 cm. above the junction of the two vertebral arteries, but it may arise either from the vertebral or from the basilar artery by a common trunk with the posterior inferior cerebellar artery. The course of the artery is obliquely backward and downward beneath the seventh and eighth cranial nerves and the flocculus of the cerebellum, where it divides into many branches which supply the anterior and inferior surfaces of the cerebellum. As it traverses the restiform body, the middle cerebellar peduncle and the flocculus, it supplies small branches to these structures. The lateral part of the biventral lobule, the flocculus and the inferior and superior semilunar lobules of the cerebellum thus receive their blood supply from this source. There are abundant anastomoses with the posterior inferior and superior cerebellar arteries.

REPORT OF A CASE

History.—One morning, soon after arising, the patient, a man aged 48, suddenly experienced dizziness, as if the room were turning from the right to the left. After this he had tinnitus, nausea and vomiting, and about two hours later he noticed that the right side of his face was paralyzed, so that he could not close his right eye or speak distinctly. He remained in bed during the next seven days because of weakness, dyspnea and slight dizziness. Then, after much persuasion, he agreed to enter the hospital.

At the age of 8 years the patient had had an "abscess of the spine," which left him with a crooked back and deformity of the chest. For the past two or three years he had been unable to work because of headaches, weakness and dyspnea, which were ascribed to high blood pressure.

Examination.—On admission the temperature was 98.6 F., the pulse rate 100, the respiratory rate 28 and the blood pressure 230 systolic and 150 diastolic. The patient was lethargic and irritable and was moderately confused. There was thoracic kyphoscoliosis, which made examination of the chest difficult. The heart was enlarged to the left; the cardiac rhythm was normal, and the aortic second sound was accentuated. There were moist rales throughout both pulmonary fields. The right pupil was 2 mm. in diameter and the left one 3.5 mm.; both reacted well to light and in accommodation and convergence. There were ptosis of the right eyelid and slight enophthalmos of the right eye. The retinal arteries were sclerotic and the optic disks slightly blurred. Visual acuity and the visual fields were normal, and extraocular movements were well performed. The right side of the face, including the orbicularis oculi and frontalis muscles, was completely paralyzed. On the right side there was complete nerve deafness and on the left side slight impairment of auditory acuity. Well sustained nystagmus

From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City-Hospital.

1. Goodhart, S. P., and Davison, C.: Posterior Inferior and Anterior Inferior Cerebellar Arteries, *Arch. Neurol. & Psychiat.* **35**:501 (March) 1936.

appeared on both right and left lateral gaze and left rotary nystagmus on upward gaze. Pain and temperature sensations over the right side of the face were greatly impaired, and over the right cheek there was also slight impairment of light touch sensation. The right corneal reflex was hypoactive. Speech was somewhat indistinct, but no dysphonia or dysphagia was noted. There was cerebellar ataxia in the use of the right arm and leg. Movements were slow and awkwardly executed; in performing the finger to nose and heel to knee tests there were dysmetria and intention tremor. The right arm was hypotonic, and Holmes's rebound sign was elicited. Gait and station could not be tested. Pain sensation was inconstantly diminished over the left side of the neck and left upper extremity, but not definitely so over the rest of the body. Muscles were equally strong on the two sides of the body. Tendon reflexes were equally active, and plantar responses were bilaterally flexor.

Laboratory Data.—Urinalysis revealed a 1 plus reaction for albumin, a specific gravity of 1.012 and an occasional granular cast in the sediment, but no red or white blood cells. The white blood cell count was 18,200. The electrocardiogram showed ectopic auricular rhythm

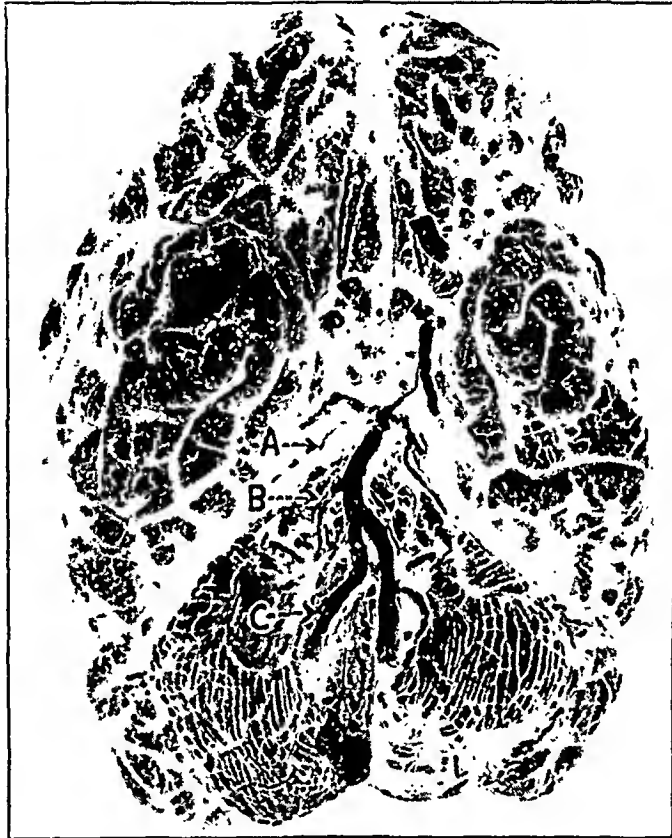


Fig. 1.—Photograph of the brain, showing (A) the right superior cerebellar artery, (B) the right anterior inferior artery and (C) the right posterior inferior artery. The dotted area includes the zone of recent infarction.

and left axis deviation. The cerebrospinal fluid showed an initial pressure of 170 mm., 122 mg. of protein per hundred cubic centimeters, 6 lymphocytes per cubic millimeter and negative Wassermann and Hinton reactions.

Course.—Despite treatment for congestive heart failure, the patient failed to improve. In the succeeding days he became more inattentive, confused and disoriented. The neurologic examination was repeated several times, with about the same results as those already recorded. During the fourth week of the illness the patient's temperature rose to 101 F., and signs of pulmonary congestion appeared. He died two days later, on the twenty-fifth day of the illness.

Anatomic Diagnosis.—The anatomic diagnosis referable to the brain was cerebral arteriosclerosis and encephalomalacia; thrombosis of the right anterior inferior cerebellar artery, with infarction of the lateral part of the medulla oblongata and cerebellum; thrombosis of the lateral branch of the left posterior inferior cerebellar artery, with infarction of the cerebellum, and multiple small softenings in the basis pontis, the midbrain and the lenticular nuclei.

Other conditions were: arteriosclerotic and hypertensive heart disease, healed bilateral pyelonephritis, benign prostatic hypertrophy and tuberculous spondylitis (?).

Gross Pathologic Changes.—The vertebral, basilar, cerebellar, and cerebral arteries were the seat of marked atheromatous change. There was an anomaly of the circle of Willis; the left posterior cerebral artery arose from the internal carotid artery and the right posterior cerebral artery from the basilar artery. The right anterior inferior cerebellar artery was completely occluded by an atheromatous plaque at the point of its origin from the basilar artery. The lateral branch of the left posterior inferior cerebellar artery was also occluded. The right flocculus and the biventral and superior and inferior semilunar lobules of the cerebellum were softened. The restiform body and brachium pontis on the right side felt less firm than those on the left. On the inferior surface of the left cerebellar hemisphere, involving chiefly the inferior semilunar lobule, was a triangular depression, 2 cm. in its widest portion and 0.5 cm. deep, where the cerebellar cortex and the subcortical white matter had been destroyed (fig. 1).

Section of the brain, after fixation in formaldehyde, showed a well demarcated area of recent softening in the right side of the cerebellum and bulb. In addition several small cystic defects, all less than 0.5 cm. in diameter, were observed in the right centrum semiovale, the anterior limb of the right internal capsule and the basis pontis on the right side.



Fig. 2.—Lower pontile level.

Microscopic Pathologic Changes.—The medulla, pons and cerebellum were sectioned serially and stained by the Weil and Nissl methods.

Level of the Midpons: This region appeared to be the highest level of the infarction. The area of necrosis was small and involved only part of the brachium pontis and some of the fibers of the right trigeminal nerve.

Level of the Nucleus of the Sixth Nerve: The right middle cerebellar peduncle, including the region of the restiform body, the spinal nucleus and tract of the right trigeminal nerve and the lateral portion of the right lateral vestibular nucleus were destroyed. In the nucleus of the right seventh nerve there was "axonal reaction" of the nerve cells, and a similar reaction was observed in the left pontile nuclei. A few of the folia of the cerebellar cortex adjacent to the pons were necrotic (fig. 2).

Level of Junction of Pons and Medulla: The right eighth nerve, the ventral and dorsal cochlear nuclei, the spinal nucleus and tract of the right trigeminal nerve, the lateral portion of the right spinal vestibular nucleus and the restiform body were all degenerated. The lesion also involved the ventral spinocerebellar tract.

Level of Midolivary Region: The lateral portion of the medulla oblongata, including the fibers of the ninth and tenth nerves and the nucleus ambiguus, was intact. The only lesion at this level was situated in the right restiform body. The nerve cells in the left inferior olivary nucleus were undergoing "axonal reaction"; many of the cells had disappeared and were replaced by foci of glia cells.

Level of Inferior Pole of Olive: Except for descending degeneration of the spinal tract of the right fifth nerve, there were no definite lesions of this level (fig. 4).

There was an advanced degree of hyperplastic arteriolosclerosis and atherosclerosis of the larger arteries. The areas of necrosis were replaced by microglial phagocytes, and in the adjacent tissues astrocytes were increased in number and size.



Fig. 3.—Upper bulbar level.



Fig. 4.—Midolivary level.

COMMENT

The clinicoanatomic correlation in this case is too obvious to require detailed comment. Suffice it to mention that the palsies of the seventh and eighth cranial nerves are the result of involvement of the respective nuclei and their nerves; the vertigo, nausea and vomiting and nystagmus are ascribed to lesions of the vestibular

nuclei and their connections with the nuclei of the vagus and oculomotor nerves; ipsilateral loss of pain and temperature sensation and corneal hypesthesia are caused by interruption of the spinal tract and nucleus of the trigeminal nerve, and the hypesthesia over the cheek is best explained by the involvement of some of the entering fibers of the trigeminal nerve. The absence of complete contralateral hypalgesia and thermohypesthesia is due to the extreme lateral and posterior position of the lesion, which spared most of the lateral spinothalamic tract. Horner's syndrome was related to the interruption of pupillodilator fibers, which are known to descend ipsilaterally from the hypothalamus and to converge in the lateral portion of the pons and medulla before continuing downward to connect with the sympathetic motor cells in the upper thoracic region.

Syndromes Resulting from Occlusion of the Cerebellar Arteries

Artery	Structures Supplied	Clinical Signs
Superior cerebellar	Brain stem Brachium conjunctivum Brachium pontis, upper portion Tegmentum of pons, lateral portion Cerebellum Anterior and posterior quadrangular lobules Superior semilunar lobule, anterior part Superior vermis Dentate, emboliform, globose and fastigial nuclei	Homolateral Cerebellar asynergia Involuntary choreiform movements Horner's syndrome Contralateral Loss of pain and temperature senses over face and body Sometimes partial deafness Sometimes weakness of face of central type
Anterior inferior cerebellar	Brain stem Brachium pontis, lower portion Restiform body Lateral tegmentum of upper part of medulla and lower portion of pons Cerebellum Flocculus Biventral lobules, lateral portion Superior and inferior semilunar lobules	Homolateral Cerebellar asynergia Horner's syndrome Deafness Complete paralysis of face Loss of pain and temperature senses over face Diminished light touch sense over face Contralateral Incomplete loss of pain and temperature senses over body
Posterior inferior cerebellar	Brain stem Restiform body Lateral tegmentum of medulla Cerebellum Biventral lobule, medial part Tonsil Inferior vermis Part of inferior semilunar lobule	Homolateral Cerebellar asynergia Horner's syndrome Loss of pain and temperature senses over face Dysphagia and dysphonia Contralateral Loss of pain and temperature senses over body

The signs of cerebellar ataxia cannot be assigned to a lesion of a single structure in the brain stem because, as is often the case in the other cerebellar artery syndromes, more than one cerebellar peduncle was involved, the inferior and the middle. Thus there was interference with both the spinocerebellar and the ponto-cerebellar system, to either of which the asynergia may have been due.

The same principles of diagnosis, so well known for the other vascular syndromes of the brain stem and cerebellum, seem to apply in cases of occlusion of the anterior inferior cerebellar artery. The onset of the disorder is usually sudden, with or without premonitory symptoms, and usually is unaccompanied by any loss of consciousness. Vertigo is the first and most important symptom and is often associated with nausea and vomiting. The other symptoms of facial paralysis, deafness, sensory disturbance and cerebellar asynergia appear in a few hours but may not all attract the attention of an unobservant patient. The diagnosis is at once obvious because of the association of signs of ipsilateral involvement of the cranial nerves and cerebellum. The clinical course is one of gradual improvement

over a variable period, and rarely is the condition fatal except as it provokes other complications, such as bronchopneumonia, or is part of extensive hypertensive vascular and renal disease. Notable by their absence are all signs pointing to involvement of the corticospinal tracts and medial lemnisci, which receive their blood supply from midline tributaries of the vertebral and basilar arteries.

As far as can be ascertained, the symptoms are related chiefly to softening of the lateral portions of the brain stem and cerebellar peduncles rather than to involvement of the cerebellar hemisphere. When an infarct is limited to the cerebellar hemisphere, vertigo may be the only clinical manifestation, or such a lesion may pass unnoticed and be unexpectedly discovered at autopsy.

The differential diagnosis of syndromes due to occlusion of the superior, the anterior inferior and the posterior inferior cerebellar artery is presented in the table.

Considering the variability of the arterial supply to the brain stem, it cannot be assumed with certainty that all syndromes caused by occlusion of the anterior inferior cerebellar artery will be identical with that in this case, but it is instructive to compare it with the syndromes in other cases. Unfortunately, Davison and Goodhart's case contributes little to knowledge of the syndrome because the arterial occlusion was incomplete and the softening limited to the cerebellum. It is to be noted that the cranial nerve signs distinguish between the anterior inferior and the posterior inferior cerebellar artery syndrome and that the extent of the sensory disturbance and the presence of homolateral choreiform movements characterize the superior cerebellar artery syndrome.

SUMMARY

The clinical and pathologic observations in a case of thrombosis of the anterior inferior cerebellar artery are presented. This syndrome is distinct from that which follows thrombosis of the posterior inferior and superior cerebellar arteries. Partial occlusion of the anterior inferior cerebellar artery is undoubtedly more common than has been believed, and it is expected that some of the distinctive features of this syndrome will permit their identification.

Neurological Unit, Boston City Hospital.

News and Comment

SCHOOL OF MILITARY NEUROPSYCHIATRY

The neuropsychiatric branch of the Surgeon General's Office announces the opening of the School of Military Neuropsychiatry at the Lawson General Hospital, Atlanta, Ga. The clinical and administrative practice of military neuropsychiatry presents many new and difficult problems to the newly commissioned neuropsychiatrist. The civilian professional experience of neuropsychiatrists varies considerably—i. e., psychoanalysis, neurology, state hospital psychiatry, prison psychiatry and child guidance—but on entering the Army they are faced with common problems, such as the selection and detection of mental misfits, the necessity for short periods of observation, puzzling and bizarre clinical manifestations peculiar to the military service and the administrative machinery set up to provide for the disposition of neuropsychiatric cases. It has been necessary, therefore, to provide some means whereby the practice of neuropsychiatry in the Army could be made more standard and uniform, to provide the individual officer with an opportunity to review subjects which he did not require in civilian life and to introduce him to the various administrative procedures which will bewilder him if no assistance is provided.

In recognition of these difficulties and to prepare the officer better for the handling of combat casualties, the School of Military Neuropsychiatry, which is unique in Army history and has already gained international attention, was developed, with the active interest and support of Major Gen. James C. Magee, the Surgeon General, and Brig. Gen. Charles C. Hillman, Chief of Professional Services, Office of the Surgeon General, to provide practical instruction for already trained and qualified specialists. Brig. Gen. William L. Sheep, Commanding General of Lawson General Hospital, a well known military neuropsychiatrist, is Commandant; the Assistant Commandant is Col. William C. Porter, also a prominent military neuropsychiatrist, who is in direct charge of the school. Colonel Porter teaches the military aspects of neuropsychiatry, on the basis of his broad experience. Dynamic psychiatry, from a military point of view, is taught by Lieut. Col. M. Ralph Kaufman, and psychiatry from an organic point of view is taught by Major Joseph L. Fetterman. Neurology is taught by Major William H. Everts. Lectures on other related subjects are given by specially selected officers, while certain members of the class relate special experiences, such as neuropsychiatry in the Air Corps, Tank Destroyer, Ranger and other special training camps. While these subjects are covered by some didactic lectures, much time is devoted to seminars and round table conferences. Clinical material of a type obtainable only in Army hospitals is provided, since experience has shown that the best method of teaching military neuropsychiatry is by constant reference to and the use of military casualties. In this manner the military administrative considerations which have presented, or may present, difficulties are thoroughly discussed. Thus the various aspects of military neuropsychiatry which confront the new officer and present difficulties to the older officers are well coordinated by excellent and experienced teachers. The advantages of mutual exchanges of experiences and opinions in the interest of uniformity and professional progress cannot be overestimated.

The quota of officers selected for each intensive four weeks' course, which began Jan. 2, 1943, includes officers from each service command and from the Air Corps, together with newly commissioned officers from training pools in general hospitals. In this manner, new officers have the advantage of the experience of older officers, and the older officers have, in turn, the opportunity of evaluating their experiences and methods in the light of experiences and methods of others. Here is demonstrated the adaptation of clinical teaching, the bedside method, to the field of military neuropsychiatry.

THE MEDICAL CORRECTIONAL ASSOCIATION

The Medical Correctional Association, an affiliate of the American Prison Association, is interested in establishing contact with all professional personnel who are specially concerned with or interested in the medical aspect of crime. Membership in this association is confined to the following groups:

(1) Physicians employed in penal and correctional institutions or jails; (2) physicians, social welfare workers and special workers who engage in medical research work in penal and correctional institutions or jails; (3) psychologists, physicians, social welfare workers and special workers engaged in medical research work in connection with (a) institutions or hospitals for the mentally ill, (b) mentally defective persons, (c) juvenile delinquents, (d)

defective delinquents, (c) outpatient or behavior clinics dealing with any aspect of crime or its prevention, (f) criminal, juvenile and domestic relations courts, (g) parole, (h) probation, (i) public and private schools, colleges and universities and (j) federal, state, county and municipal public health organizations; (4) any other person who, while not automatically falling in any one of the three aforementioned groups, presents satisfactory evidence that he or she is engaged in research or an occupation in which the medical aspects of crime are acknowledged as important features.

The annual dues of the association are \$1, and their payment entitles the member to vote in the elections, to present papers before the open meeting of the association and to receive copies of the minutes, by-laws and abstracts of papers which have been presented at the annual meeting.

The present officers of the Medical Correctional Association are: president, Dr. J. D. Reichard, United States Public Health Service Hospital, Lexington, Ky.; first vice president, Dr. John W. Cronin, United States Public Health Service Hospital, Sheepshead Bay, N. Y.; second vice president, Dr. Lawrence Kolb, Assistant Surgeon General, Washington, D. C.; secretary-treasurer, Dr. Robert M. Lindner, Federal Penitentiary, Lewisburg, Pa.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

GEORGE A. BLAKESLEE, M.D.

President, New York Neurological Society, in the Chair

Joint Meeting, Oct. 6, 1942

Presidential Address: Neuropsychiatry in Wartime. DR. GEORGE A. BLAKESLEE.

This address was published in full in the December 1942 issue of the *Bulletin of the New York Academy of Medicine*, page 775.

Early Laminectomy for Injury of the Spinal Cord. DR. FOSTER KENNEDY, DR. PETER G. DENKER and (by invitation) DR. RAYMOND L. OSBORNE.

The controversy over whether laminectomy should be performed more frequently in cases of injury to the spinal cord is reviewed, and a study of the literature is presented. There has been a pendulum-like swing from conservatism to radicalism and back to conservatism again. At present most neurosurgeons seem to be excessively conservative in the treatment of this condition. Five illustrative cases in our experience at the Bellevue Hospital are presented. In all these cases severe injury to the cord had been sustained, and, because of the apparent hopelessness of the situation, the neurosurgeons were reluctant to operate. However, they were finally persuaded to perform laminectomy, since we felt that nothing was to be lost, and possibly something might be gained, by such a procedure. In all these cases definite lesions were encountered, which were helped by the surgical intervention. Scarring, fractures of laminae which did not appear in the roentgenogram, spicules of bone within the substance of the cord and other lesions were discovered when the cord was exposed; so it was felt that operation had really contributed a great deal to recovery in these cases. We therefore advocate more frequent laminectomy in cases of injury to the spinal cord, for the following reasons:

1. It is impossible to determine from neurologic examination at the time of the accident whether the cord has been completely severed or whether function has been physiologically interrupted.
2. Roentgenograms of the spine are by no means conclusive as to the presence of fracture of the laminae; on the other hand, spicules of bone may be pressing on the cord without appearing on the roentgenogram.
3. In the presence of manometric block, laminectomy should always be performed, regardless of whether it is felt that the injury to the cord is complete or not.
4. The operative mortality associated with laminectomy is so low that it should not be a factor in decision to operate. The operation is much less dangerous than is a diagnostic laparotomy.
5. No statistically followed series of cases has yet been reported in which treatment with laminectomy was employed in alternate cases. Such a study is advocated to decide the merits of this operation.
6. When operation is decided on, laminectomy should be performed early, since a case of injury to the spinal cord is a surgical emergency, and a delay of two to six weeks for "spinal shock" to subside is a needless waste of time.

This article was published in the April 1943 issue of the *American Journal of Surgery*.

DISCUSSION

DR. JOSEPH E. J. KING: There are probably two types of injury to the spinal cord for which one can decide to operate almost immediately, even without roentgenographic examination: first, a condition in which paraplegia has been produced by a direct blow on the back, directly over the spinous processes, such as a blow with a hammer, a fallen stone, a large shell

fragment, a piece of concrete, or a blackjack. The trauma to the cord, most likely, is due to crushing of the spinous processes and laminae, so that these bony structures impinge directly on the cord. It goes without saying that immediate operation is indicated. Second, gunshot wounds and stab wounds of the back producing paraplegia. In some cases of such injury rapid recovery may take place, but in many no improvement will occur, especially when the injury is produced by high velocity missiles. In a few cases observed during the first World War complete clinical division of the cord was produced by the rotary motion of such missiles, which merely went through the soft parts without touching the cord or even injuring the vertebral column. In other cases of gunshot and stab wounds the cord may be completely divided. Nevertheless, one is justified in making early exploration in the hope that only a lesser injury of the cord may be encountered.

The first laminectomy I ever witnessed was done by Dr. William A. Downes at the General Memorial Hospital in the summer of 1911. A well developed girl about 13 years of age had received a bullet wound in the back at about the level of the sixth dorsal segment. She was brought to the hospital completely paralyzed below that level. Dr. Downes observed that the .22 caliber bullet had passed through the dura in the midline and that the distal end of the bullet just protruded through the dura into the posterior longitudinal fissure, so that it had separated the posterior column, almost as though with a pair of blunt forceps. In February 1912 a photograph was received from the girl, in Canada, which showed her playing and throwing snowballs in the snow. She had completely recovered. Had the bullet not been removed, she might not have lived, and had operation not been done immediately, I think she would have been paraplegic, at least for a long time.

Most of the injuries to the spinal cord of the other type are associated with fracture or fracture-dislocation of the spine. As Dr. Kennedy stated in his paper, cases of fracture-dislocation in the cervical region are excluded, which leaves a rather large number involving the dorsal and lumbar regions of the spine. As Dr. Kennedy mentioned, neurosurgeons have been hesitant to perform early operation in cases of such injury—I believe for good reasons. Ordinarily the surgeon is ever ready to operate when he feels that any good will come of it. The reluctance to operate early is derived from experience of years, in which in a number of cases the cord has been found to be completely dissolved and the procedure useless. On the other hand, many patients have completely recovered, or improved to a considerable degree, without operation, provided the deformity was corrected.

I remember a patient whom Dr. Kennedy saw, a woman about 79 years of age. The automobile in which she was riding ran off the road and struck a tree, and she was thrown forward, receiving a horseshoe-shaped laceration of the scalp, which amounted to a partial avulsion. She had complete quadriplegia. She was brought to Lawrence Hospital, Bronxville, N. Y. One neurosurgeon wanted to operate, although roentgenograms showed no deformity of the cervical portion of the spine. The son of the patient, who was a surgeon, and Dr. Kennedy objected. No operation was performed. The patient was turned in bed, like a duck on a spit, and was catheterized by her son twice a day. After a while she began to move her arms, and finally the quadriplegia completely disappeared, with the exception of a slight residual paresis in the ulnar region of the left hand. I visited her in her home, and to all intents and purposes she had made a complete recovery.

Then in 1918, during the first World War, I saw a soldier who had been playing football; in making a flying tackle, which was allowed in those days, he was injured. The neurologists and surgeons did not think he should be operated on. There was no complete block. He recovered rather promptly and within three months was out of the hospital, walking about as well as ever. The level of his injury was about the eleventh dorsal segment.

These 2 cases represent what every neurosurgeon has seen, some rather frequently. On the other hand, all have seen instances in which the cord was completely divided, or if not, was so attenuated that it looked like two pencil points placed together, so that anatomic division had practically resulted. In view of these facts, the surgeons have shied away for the most part from immediate operation and prefer to effect correction of the deformity and wait, in most instances, for improvement.

A number of years ago Dr. Alfred S. Taylor and Dr. Claude Coleman told me that indication for immediate operation in a case of injury to the spinal cord depended, in their opinion, on the presence of complete block. I do not think that is right; nevertheless, it is what used to be taught. At times complete block may exist without destruction of the cord, and it is doubtful whether operation would be of benefit. On the other hand, it is possible that a spicule of bone may be driven into the cord, as Dr. Kennedy stated, without complete block. Therefore the rule of operation only for complete block does not hold.

Stereoscopic roentgenograms of the spine are not generally made, but there is no legitimate reason for not doing so. It is surprising how well one can visualize the component bony structures forming the wall of the spinal canal with such exposures, while in flat roentgenograms little detail can be seen. Really good roentgenologists, like Dr. Dyke and Dr. Law, would not think of reading roentgenograms of the skull unless they were stereoscopic, but for some reason most men are not accustomed to making stereoscopic roentgenograms of the spine. Stereoscopic roentgenograms of the spine show up just as clearly as do those of the skull. Therefore in all cases of injury, as well as other lesions, of the vertebral column with which I have anything to do I insist that good stereoscopic plates be made.

With regard to gunshot wounds in the first World War: In the neurologic services, and I do not know whether Dr. Stookey will bear me out or not, my associates and I encountered three main types of injury—those of the head, those of the spine and those of the peripheral nerves. We had a great many cases of injuries to the head, and an even greater number of injuries to the peripheral nerves, but few of injury to the spinal cord. Most of the men with such injuries died before they reached our hospital, and if they did not, quite a number died after arrival there. These deaths were due to ascending infection of the kidneys, or other infection, and a number of the patients gradually “faded out.” As a whole, the group was a very poor one, and we had little success with them. Just what effect the sulfonamide drugs would have had in preventing the infections is not known. It is quite probable that more men with gunshot injuries of the spine in the present war will be operated on, with improvement, than in the last one.

Another point to be borne in mind can be illustrated by a case which I had not long ago at Bellevue Hospital. The patient, a young man, had a rather severe injury to his back, and paraplegia immediately developed. I saw him two or three weeks after his injury, at the hospital, and he had many severe bed sores. Lumbar puncture revealed complete block, and iodized poppyseed oil showed the obstruction. Laminectomy revealed a large central herniation of an intervertebral disk pressing against the cauda equina firmly, and to a severe degree. He made a complete recovery after removal of the disk.

One of the greatest additions to the methods of treatment of injuries of the spinal cord is Munro's tidal drainage. All are acquainted with the fact that in the past many patients with such injuries died not of injury to the cord per se but, rather, of ascending infection of the kidneys, from the bladder.

If an early operation is done, it should, and can, be performed readily with local anesthesia, especially since half the field is already anesthetic.

In conclusion, I wish to say that we surgeons are willing to operate in certain cases early, or immediately, provided the neurologists can show definite reasons for doing so. We are not lazy, and we are glad to do the work when we are convinced that better results would thus be obtained. I feel sure that in some cases immediate operation should be performed, that in many cases no operation is required and that in others, even if operation is carried out, little improvement will result.

DR. BYRON STOOKEY: Dr. Kennedy cited Sir Charles Bell; as I recall, Bell advised against operation. He objected to one's comparing the removal of a piece of bone which is pressing on the brain with the same procedure in relation to the spinal cord. He called attention to the fact that a piece of bone presses only on a small amount of the total substance of the brain, while as a rule it presses on the total substance of the spinal cord.

Dr. Kennedy stressed the brilliant experiments of Allen, which raises a point of especial interest in the present discussion. There is in the dog no extra room within the vertebral canal or around the dura, such as exists in man. In man there is a large factor of safety in the relative sizes of the spinal cord, the dural sac and the vertebral canal, so that the spinal cord in many parts of the vertebral canal can swell to almost twice its normal size and still not be impinged on by the surrounding structures. Allen's recommendation of making multiple incisions in the dorsal portion of the cord I should consider of doubtful application to man because of the difficulties involved, the bleeding that would attend it and the disruption of part of the function of the dorsal column that would result. However, if by so doing the major portion of the function of the spinal cord could be regained, I should think it worth the doing.

The problem is not that the surgeon is afraid or unwilling to operate or that the operation is difficult; rather the question is whether he can improve the patient's condition. I agree thoroughly with the recommendations by Dr. Kennedy and Dr. King with regard to gunshot wounds of the spinal cord, for which much more can be offered by exploration than by waiting. The wound can be cleaned out and *nettoyage* of the field done, and perhaps foreign bodies can be removed and the cord given whatever chance it may have to recover. Most neurosurgeons would be inclined to operate under such conditions, the operation, of course,

being preceded by stereoscopic roentgenographic study, as Dr. King indicated. On the other hand, if the bullet tract is filled with minute spicules of bone that can be seen within the vertebral canal, operation might be inadvisable.

Dr. Kennedy cited the case in which Dr. Stetten operated. I remember his reporting that case before the New York Surgical Society some years ago, and I think all are agreed on operating in such cases. If I recall correctly, the man was hit on the back of the neck by a blackjack, with fracture of the arches of certain cervical vertebrae. Stereoscopic roentgenograms would have shown this had they been taken. I think one is justified in operating in cases of injury to the cord from a direct blow. Neurosurgeons are in accord as to the advisability of exploration in such cases, but they are relatively rare in civilian life, especially those of injury from gunshot wounds. The majority of cases are those in which a deformity has been produced by jackknifing and compression. By operation the surgeon can only relieve the pressure on the cord; he can do nothing more for the damage to the cord except clean up the wound. By removal of the arches he still leaves severe angulation of the bodies of the vertebrae, and the angulation of the bodies is often more damaging to the remnants of the spinal cord than operative removal of the pressure. The principle of treatment is to remove the pressure on the cord, and more recent advances in the methods of reduction offer the patient more than operation can, for if the reduction is well done, it not only reduces the pressure on the dorsal aspect of the cord but removes the compression of the ventral aspect, which is much sharper and of greater significance. With Crutchfield's tongs, attached in a small hole in the outer table of the skull, traction can be applied in a few minutes, and reduction accomplished without operation. When the pressure that is causing the difficulty can be removed by skeletal traction and reduction without operation, there is the possibility that a stable vertebral column will be established. When the arches are taken off, and the laminectomy must, of necessity, involve a minimum of three vertebrae in order to accomplish any reduction of pressure, one has removed certain factors making for stability of that portion of the spine. Because the surgeon feels he can do nothing to improve the patient's condition except remove pressure, he prefers to remove that pressure by skeletal traction and other methods of reduction. By these means I have been able to reduce decided deformities of the spine, and hence I think the nonoperative approach is the more desirable.

The manometric test indicates only an obstruction. That obstruction may be mechanical, due to displaced vertebral fragments, or it may be caused by edema. Edema cannot be relieved by the surgeon. He can only make more room by opening the dura, and thus relieve the pressure caused by the edema. With the modern use of hypertonic solutions, which formerly were not available, but which I think should be used in cases of acute injury to the spinal cord, and have been so employed in Dr. Scarff's service at Bellevue Hospital, this edema can be relieved. Therefore the presence of edema is not, I believe, a valid indication for operation. No one here can be a more enthusiastic supporter of the manometric test in diagnostic procedures related to the spinal cord than I am, but for edema it is of doubtful value, for while it does indicate a block, that block may be due to edema, which can be relieved conservatively by use of hypertonic solutions. We surgeons have a great deal of respect for the spinal cord and the ease with which it is damaged, and, when damaged, the ease with which any remaining function may be further jeopardized; hence our conservative attitude has a great deal to commend it in certain cases at least.

I had an opportunity to review the 5 cases which Dr. Kennedy has cited here. In the first case there was probably a unilateral dislocation. An operation was performed; perhaps Dr. Kennedy or Dr. Denker can tell whether any attempt was made to reduce the offending dislocated vertebra. Certainly, that should have been done first. I have had to operate in cases of unilateral dislocation because I could not get a reduction otherwise. Even then, in 2 cases I was not able to obtain a reduction by placing a lever underneath the arch, and I had to open the lamina in order to relieve pressure on the cord.

DR. PETER G. DENKER: I do not believe any attempt was made to reduce the fracture first.

DR. BYRON STOOKEY: I think it should have been done. In 1 of the other cases the injury was a gunshot wound, and I should certainly have operated in this case. Another case cited was that of Dr. Stetten in which the man was struck over the back of the neck with a blackjack and had a fracture of a posterior arch. In that case I believe an operation should have been done. In 1 of the other cases a pregnant woman tripped and fell forward on the floor; she got up and was able to walk; a week later she noted numbness of the legs, and subsequently there developed a sensory level from the twelfth to the tenth thoracic. She was operated on, although roentgenogram did not show any dislocation. I do not believe Dr. Kennedy saw this patient, and I wonder whether there was actually an injury to the cord. I have never known of any patient falling forward and damaging the spinal cord. It has

always been a jack knife fall that has done it. I wonder whether the case could have been one of myelitis or infection.

DR. PETER G. DENKER: The woman had complete block on two successive days.

DR. BYRON STOOKEY: I appreciate that. I shall never forget an operation which I performed with Dr. Taylor on a woman in whom transverse myelitis developed overnight. She had a large, swollen cord. Dr. Kennedy and his associates will have to demonstrate the injury to the cord in this case; I do not believe it is substantiated in the report. In the other case there were multiple displacements, apparently involving several lumbar vertebrae; at operation, and wisely I believe, the dura was not opened. It is wise sometimes not to open the dura, for, in my experience, when the dura is opened the damaged cord may ooze out, so that, as Dr. King said, whatever chance the patient has, and probably there is none, is taken away.

Dr. Taylor has been cited here as one who advises operation. From my experience with him in the last ten years of his practice I know he did not recommend surgical intervention, for he had evolved one of the best methods of closed reduction which was available at that time. He advised me strongly against operative procedures. We saw a patient at the Beekman St. Hospital, and I did the operation. I did not reduce the fracture but, rather, did a decompression and I kept the patient under observation until he died, about fifteen years later. He had pronounced wedging, in which the anterior surface of the wedge was 4 to 5 mm. in thickness, a severe deformity, and whatever chance the man may have had I must have taken away from him. So, in summary, I do not believe that in these 5 cases Dr. Kennedy has presented enough evidence to warrant a change in opinion on the part of any surgeon who disagrees with him. I agree that gunshot wounds, at least in the early stage, should be explored after study unless there is some contraindication, and that the wounds resulting from direct blows, with fracture of the posterior arches, should likewise be explored, but I question seriously the value of attempting to remove pressure from the cord by operation, which is all the surgeon can do, when the real deformity is in the body of the vertebra. I believe the operation only weakens the vertebral column.

DR. FOSTER KENNEDY: I rather thought I had forestalled this argument by saying at the beginning that dislocations did not come into consideration here.

DR. BYRON STOOKEY: Subluxations are different from real dislocations.

DR. FOSTER KENNEDY: Of course I mean subluxations—one can hardly reduce a dislocation. With a subluxation of the vertebral column one ought to try to make a closed reduction. The case of the elderly woman that Dr. King spoke of is a perfect example. She was treated with prolonged hyperextension, and although she had been paraplegic at the beginning, she had at the end, as Dr. King said, slight involvement of only one hand. When I went in to see her she was on a high catafalque in a great room. Her son had told me what a good patient she had been. I approached the catafalque cautiously in the gloom and said to her, just to break the ice: "Mrs. X, I hear you are a very good patient." She was totally paralyzed and could not turn her head, which was in hyperextension; so she turned her eyes sharply to the right and looked at me and said: "Dr. Kennedy, when one is 80 years old, and paralyzed in all four limbs, there is nothing left for one but virtue." A person like that could scarcely help getting well.

Sir Charles Bell's ghost was evoked in our paper merely to give it respectability by historical reference. His opinions, however fine his mind was, can hardly be of great value now, in view of the neurosurgery of his day. I do not feel that neurosurgeons have a sufficient regard for themselves. They view themselves in a diminishing mirror, so that they seem to themselves—or is it to each other?—too small. We physicians think them potent and important and feel they should go about their business a little more urgently. Dr. Stookey will, I am sure, subscribe to the idea that the urging on the part of the physician to explore the known level of spinal disease has revealed a great many pathologic, and often curable, situations. That is exactly my point in this argument: the surgeon cannot tell beforehand what he may find. If he knows he is dealing with a subluxation or a dislocation, it is his duty to reduce it if possible, but if he does not know what the situation is, it is his duty to explore. He does not know what the situation is until he has looked. Another thing, Dr. Stookey's criterion for operation is: "What can be done to improve the condition?" One cannot tell what one can do to improve the condition until one explores. A pontifical statement that the cord is smashed beyond repair may be wrong. I know instances, such as those cited in this paper, in which I believed the patient would not have recovered had exploration not been done. Then, too, the patient must be considered. I remember a young physician who had, I believe, a completely smashed cord. I had advised operation at the time of the injury. A surgeon had advised against it, and the man was not operated on. He remained paraplegic

and very ill for a year; he was extremely unhappy and disturbed because he felt that no one knew the state of his spinal cord for certain. At the end of about a year, I advised the physician to submit to operation on the spine, although I did not believe that any benefit would result, as there did not. The cord was pulped at the level of the lesion, but after operation and the securing of certainty the patient completely changed as a human organism. His adaptation to his incurable condition became perfect almost overnight; he knew exactly where he was. Such is the value of certainty and decision in giving peace and power with which one may deal with a lamentable situation. I told the patient before the operation that I looked on the laminectomy as a psychologic treatment, that I did not think it would do him any physical good, but it might help his emotional adjustment.

Effect of Vitamin E Therapy on the Central Nervous System in Amyotrophic Lateral Sclerosis. DR. CHARLES DAVISON.

In 10 cases of amyotrophic lateral sclerosis treatment was instituted with vitamin E and alpha tocopherol, and, except in 1 instance, there was no clinical response to this therapy.

Histologically, however, in 6 of the cases in which intensive treatment had been carried out destruction of the myelin sheaths and axis-cylinders was much less severe than in the cases in which no treatment was given. The dense gliosis which is usually present in amyotrophic lateral sclerosis was diminished, or almost absent, in the cases in which vitamin E was administered. The lessened destruction of myelin sheaths and axis-cylinders and the faint gliosis in these instances were perivascular and insular. In 1 of these cases the beneficial changes were limited to one side of the cord only. The nerve cells of the involved bulbar nuclei and the anterior horns remained unchanged and showed no signs of reversibility.

The histopathologic process in the other 4 cases, in which treatment was less intensive, was concluded to be similar, although less extensive, to that in cases in which no treatment was given.

There is a possibility that vitamin E therapy in cases of amyotrophic lateral sclerosis resulted in a reversal of the degenerative reaction, affecting simultaneously and equally the myelin sheaths, the axis-cylinders and the glia.

DISCUSSION

DR. TRACY PUTNAM: This is an interesting approach to the subject of amyotrophic lateral sclerosis, and Dr. Davison's beautiful preparations speak for themselves. On the basis of my own experience I feel he is unquestionably right that there is a stage of myelin degeneration which is reversible. This can be clearly shown in animals. If one induces demyelination of axis-cylinders in one area, which can be done in any one of several ways, and follows the animals for a time, killing them at intervals, it is quite clear there is a reversible stage of damage to the myelin, and then an irreversible stage. In no animal I have seen, and I think Dr. Ferraro has had the same experience, has there been any return of myelin after complete removal from the axis-cylinders, even after periods as long as fifteen months. If this does not happen in animals, I am skeptical about its occurring in human beings. All agree with Dr. Davison that when the axis-cylinder is actually interrupted regeneration cannot be expected, but when the axis-cylinder is continuous, and merely swollen or tortuous, the process may be reversible.

Dr. Davison has presented some new data which deserve to be closely scrutinized, but they are perhaps open to another interpretation. In a recent survey of all the cases of amyotrophic lateral sclerosis in the records of the Neurological Institute, Dr. Roy Swank and I found that the picture was extremely variable, and that there was every gradation between the classic Charcot type, with atrophy of the hands and spasticity in the legs, and spinal muscular atrophy, on one end of the scale, and, on the other, the rather rarer type of lateral sclerosis. In cases in which no treatment had been given, we found that the prognosis was far worse for the classic form, with well pronounced signs of involvement of the pyramidal tract. The prognosis was much better if the disease was atypical, and as all know, for the pure lateral sclerosis or the pure muscular atrophy the prognosis was not poor.

The notes show that in the 6 cases in which less than average demyelination was present, the signs referable to the pyramidal tract, even before treatment was started, were rather insignificant. There was a negative Babinski sign in cases 1, 2 and 3; in case 4 there was a positive Babinski sign; in case 5 the signs referable to the pyramidal tract were relatively mild, and in case 6 they were not extreme. In 3 of the cases the symptoms were chiefly bulbar, and the patients died of pneumonia. It seems quite possible that in these cases more amyotrophy and less defect in the pyramidal tract were present from the beginning, and that is perhaps why fewer changes were evident in the lateral column. Dr. Davison's analysis has

shown that all the changes are associated, and this is a rather general rule in neuropathology. If there is degeneration of myelin there is gliosis also, unless some nutritional lack prevents it. The fact that no loss of myelin and no gliosis was noted in these cases suggests there had never been loss of myelin to the extent seen in the other cases. I note that in the second group of 4 cases there were, even before treatment, evidences of serious defects in the pyramidal tracts and, in proportion, rather fewer bulbar symptoms. I should like, therefore, to ask Dr. Davison whether it is possible that from the beginning the first group of cases differed from the average, or classic, case.

DR. ISRAEL WECHSLER: Like Dr. Putnam, I do not know just what to make of the slides which Dr. Davison showed. It is difficult to draw conclusions concerning recovery from microscopic sections taken at autopsy. I saw the slides for the first time tonight, and it has all come as a surprise. Evidently, Dr. Davison has demonstrated less degeneration in treated than in untreated patients.

From a clinical point of view it is clear that the vast majority of patients do not respond to treatment. I shall soon have complete records on 70 patients, about 60 of whom showed no improvement; the rest did. Several of them, some of whom I presented at a meeting of this society two years ago (*Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E*, *ARCH. NEUROL. & PSYCHIAT.* **45**:873 [May] 1941), are still living. They are not very good specimens of health, but they are alive. It is my opinion that amyotrophic lateral sclerosis is not one disease, but a series of syndromes. There is an inflammatory type, as Wimmer showed long ago. In a great many cases the disease has a vascular origin. A small number of cases may belong to the group of deficiencies. It is known that vitamin deficiency causes "degenerative" changes, and since the pathologic process in amyotrophic lateral sclerosis resembles that seen in avitaminosis the inference may be justified that deficiency also plays a part in some cases at least. Whether this is true I do not know, nor am I certain that one is dealing with a vitamin E deficiency in my cases. There is some evidence that an X factor operates in some cases.

My associates and I are still working with patients despite the discouraging results of the past two years. We know, for instance, that hypodermic injection of tocopherol is no better than, and perhaps not as good as, oral administration. With a test perfected by Drs. Sobotka and Mayer the uptake of tocopherol in the blood can be measured. It seems that the blood curve does not rise with doses over 100 mg., no matter how much is administered.

My own interest in the question of degenerative processes in general is even greater than in amyotrophic lateral sclerosis itself. All know how unsatisfactory the word degeneration is—that it is an autopsy diagnosis *in vivo*. What one means by it is disappearance of nerve cells, myelin and axis-cylinders, and replacement with glia tissue in some cases. The underlying dynamics of the production of degenerative processes is not understood. Whether the slides shown here contribute to one's knowledge, whether they point to less "degeneration" or to a difference in reparative processes is a matter of opinion.

It seems to me that characteristic of amyotrophic lateral sclerosis is a discrepancy between the functional, or neurologic, picture and the anatomic substratum. One may observe severe degeneration of the pyramidal tracts on section and record few signs during life. It is known how frequently a Babinski sign is lacking and the abdominal reflexes are present despite tremendous involvement of the pyramidal tracts. In a measure, this is true of the discrepancy between functional and structural impairment in multiple sclerosis. One often observes a white optic disk which should cause total blindness, and yet the patient has fair vision. The usual explanation is that the preservation of the axis-cylinder permits function to continue, but that is not always true.

In conclusion, I should like to feel happy about Dr. Davison's demonstration, and I hope that what he said is valid. I can only repeat that I think a small proportion of cases of amyotrophic lateral sclerosis belong to the vitamin deficiency group, but that remains to be proved.

DR. A. M. RABINER: This presentation by Dr. Davison adds to the perplexity that began when I listened to Dr. Wechsler's original paper two years ago. At that time I questioned the basis for the therapy recommended because the rats which had been studied for sterility had, as a result of vitamin E deficiency, shown muscular atrophy and weakness. This was supposedly due to disease of the pyramidal tract. My perplexity arose from the fact that there is considerable doubt whether the rat has a tract that can be called the pyramidal tract. There are some fibers in the rat's spinal cord that have been so labeled. It is questionable whether this is correct for animals that are predominantly quadruped. The horse and sheep have few pyramidal fibers demonstrable in the brain after excision of the motor cortex and no pyramidal tract fibers demonstrable below the cervical level in the cord. Because of this, I thought it

more likely that therapeutic improvement in cases of amyotrophic lateral sclerosis was ascribable to the influence on the anterior horn cells than on the pyramidal tracts. Some of my associates, later, after having given a number of patients vitamin E, concluded that some of the fibrillations disappeared and the patients themselves seemed subjectively better. Now Dr. Davison presents pathologic material demonstrating no changes whatever in the anterior horn cells after vitamin E therapy, but some possible improvement in the appearance of the pyramidal tract.

DR. CHARLES DAVISON: Like Dr. Putnam, I have in a previous paper (*Amyotrophic Lateral Sclerosis: Origin and Extent of the Upper Motor Neuron Lesion*, ARCH. NEUROL. & PSYCHIAT. 46:1039 [Dec.] 1941) emphasized the pathologic and etiologic variability in cases of amyotrophic lateral sclerosis. In this, and in other papers, I showed that the demyelination in a number of cases of amyotrophic lateral sclerosis is not limited to the pyramidal tract but may extend to the other ventrolateral tracts or to the posterior column. Since this communication I have reviewed 36 other cases of the disease in which necropsy was performed, cases studied clinically by competent observers and recognized as true instances of amyotrophic lateral sclerosis, and have found only 2 in which the demyelination could not be seen in the gross myelin sheath preparations. One of these 2 cases, because of mental symptoms and some extrapyramidal features, was considered an instance of spastic pseudosclerosis.

In reviewing the 6 cases, as Dr. Putnam did, it should be emphasized that absence of the Babinski sign in amyotrophic lateral sclerosis does not mean absence of a lesion of the pyramidal tract. In this illness there is disease of the anterior horn cells and of the pyramidal tract. In many cases of amyotrophic lateral sclerosis, because of the disease of the anterior horn cells, reflexes may not be exaggerated or pathologic. Exaggeration or intactness of reflexes in the presence of disease of the anterior horn cells signifies only one thing, disease of the pyramidal tract.

In cases of progressive spinal muscular atrophy, purely a disease of the anterior horn cells, the reflexes cannot be elicited at all, for here pyramidal degeneration cannot be demonstrated.

DR. HENRY A. RILEY: Did the patients have any weakness?

DR. CHARLES DAVISON: Yes, all the patients had weakness, atrophy and fibrillations.

In cases 1, 2, 3, 5 and 6 hyperactive reflexes and diminished abdominal reflexes were noted. There were a positive Babinski sign in the fourth case and a bilateral Hoffmann sign in the sixth. Of the 4 so-called control cases, no Babinski sign was elicited in the ninth and tenth. I believe that the changes in these 6 cases should not be interpreted as pathologic variations of amyotrophic lateral sclerosis. Why should they have occurred in succession and in such large numbers just when the treatment was given? It could not be a mere coincidence. The lack of gliosis, I agree with Dr. Putnam, is difficult to explain, but it is what I saw.

PHILADELPHIA NEUROLOGICAL SOCIETY

F. H. LEWEY, M.D., *Presiding*

Regular Meeting, Oct. 23, 1942

Primacy of Area 13 of the Orbital Surface of the Cerebral Cortex in the Production of Hyperactivity in Monkeys. DR. HENRY A. SHENKIN and DR. THEODORE C. RUCH.

Bilateral ablation of the posterior orbital gyrus, which Walker recently differentiated as a new cytoarchitectural area (area 13) and which Bailey, Baemer and Sweet demarcated physiologically from adjoining areas, was performed in a series of monkeys. This procedure produces in a notable degree many of the symptoms that have been described for prefrontal lobectomy by various workers. They are as follows:

1. Hyperactivity is manifested by long-continued, methodic pacing or running of a regular, stereotyped character.

2. Hyperactivity from lesions in area 13 is quantitatively great, is consistently obtained and is always manifested in some degree within even the first or the second postoperative day, whereas similar hyperactivity from other prefrontal areas is said to be delayed in onset (as long as two to three weeks) and does not invariably occur. For these reasons it is concluded that area 13 is a focal representation which controls the activity level of the monkey.

3. Other motor activities are not marked by hyperactivity, but rather suffer reduction. Random, spontaneous activities and posturings are reduced in variety and in quantity, as is emotional expressiveness. There are also certain ill defined behavior changes. All of these symptoms are most evident in the first postoperative week.

4. Hyperactivity is accompanied by loss in weight and a slight increase in food intake.

DISCUSSION

DR. SARAH S. TOWER, Baltimore: This paper is interesting to me because it explains why I have been failing for some years to obtain, with electrical stimulation of the frontal lobe of the monkey, a type of response which is so readily and strikingly obtained in the cat, that is, arrest of spontaneous movement.

There is, of course, an enormous difference between the cat's and the monkey's prefrontal lobe. The cat has almost none, and what it has is cytoarchitecturally undeveloped. All of it is fairly readily accessible and I have stimulated the whole, but in the monkey I never have stimulated the orbital surface. I have been able to stimulate only the dorsal and lateral surfaces of the frontal pole, either by exposure or with implanted electrodes. Under these circumstances, I have rarely been able to demonstrate in the monkey a result which is most striking in the cat, inhibition of spontaneous activity.

In these experiments with the cat, the frontal pole is exposed with the animal resting on a stand and under very light ether anesthesia. Under these circumstances, there may develop spontaneous rhythmic wagging movements of the tail, chewing movements of the jaw, running movements involving all four extremities, nystagmoid movements of the eyes or other rhythmic movements, which one can count on to be continued for minutes, or perhaps indefinitely. Stimulation of the frontal pole, then, depending on the strength of the stimulus, will slow such movement or arrest it, and hold it in arrest, until stimulation is discontinued. Thereafter, the movement will resume, often with a poststimulatory escape, like a rebound phenomenon.

In the monkey I had expected, because of Dr. Richter's and Dr. Hine's previous results with bilateral frontal lobectomy, to find a similar electrically excitable effect, but there was none. There is another inhibitory action against spontaneous movement, both in the monkey and in the cat: a quieting effect, which is generally distributed. But I could never find in the monkey's cortex the powerful arresting effect so conspicuous in the cat. However, I never stimulated the orbital surface of the frontal lobe, because of technical difficulties.

I should like to ask the authors what they know of the cytoarchitecture of area 13. Is it a developed type of cortex, or is it primitive, like the whole prefrontal lobe in the cat?

DR. H. A. SHENKIN: As I understand it, it is a primitive cortex, not at all developed. It is merely a small subdivision of the general prefrontal cytoarchitecture.

DR. SARAH S. TOWER, Baltimore: What is the ratio of the supragranular to the infragranular layer? In the cat the whole prefrontal area has a poorly developed supragranular layer.

DR. H. A. SHENKIN: To be frank, I am not sure what the ratio is for this area. That the area is really well delineated is supported by the fact that Bailey and Sweet have recorded specific stimulatory effects from this region.

DR. SARAH S. TOWER, Baltimore: It is from this area that they got the changes in respiration, is it not? The whole prefrontal lobe of the cat, which appears to be a unit, can slow or arrest respiration.

DR. H. A. SHENKIN: Bailey and Sweet found the effects on respiration to be particularly limited to this cytoarchitectural area, and this is physiologic evidence for the validity of the differentiation.

DR. SARAH S. TOWER, Baltimore: I wonder if one can consider area 13 in the monkey the homologue of the carnivore's entire prefrontal lobe, and all the other areas—9, 10, 11, 12 and the 40's, all highly developed cytoarchitecturally as something added.

DR. H. A. SHENKIN: As I recall, area 13 is just as well developed as any of the surrounding areas. These areas are certainly not as primitive as the prefrontal cortex of the cat, but in relation to other regions of the monkey brain area 13 is not a developed cortex. However, specific localization to this area in the monkey is certainly conceivable.

DR. SARAH S. TOWER, Baltimore: Not much is known of the phylogenetic development of this region, is there?

DR. H. A. SHENKIN: I don't know much about it, anyway.

DR. B. J. ALPERS: I should like to ask Dr. Shenkin whether, with destruction of area 13, there is any change in the emotional reactions of his monkeys. I ask this because of the association in the minds of some persons between lesions of the frontal lobe and loss of aggres-

sive tendencies. I wonder, also, whether the overactivity which he describes is pure overactivity, or whether it represents loss of inhibition or a personality change on the part of the monkey which is expressed in overactivity.

DR. H. A. SHENKIN: We did not ablate areas other than 13 in these animals. However, it is not an uncommon experience of other workers who have ablated the entire prefrontal lobe to observe diminution of activity in the first few weeks, followed by hyperactivity.

Such an effect makes one wonder, perhaps, if there had not been ablated in addition an excitatory area, which resulted in inhibition of activity—for example, area 8, which Dr. Kennard has ablated in many animals. Her animals sit with their heads between their shoulders and will not indulge in any voluntary activity; this inactivity is followed, if further removal of the prefrontal lobe is carried out, by hyperactivity. There was no change in respiratory rate that we could notice. Oxygen consumption was not altered from that before operation.

Fulton and Watts (*Ann. Surg.* 101:363 [Jan.] 1935) reported cases of intussusception in animals with prefrontal ablations. In our experiments, in which we measured the time required for carmine to pass in the feces, we could demonstrate no change in gastrointestinal motility. Accurate measurement revealed a slight increase in food intake, which could be accounted for by the increase of activity rather than by any metabolic alteration. We could detect no metabolic changes in our animals.

DR. SARAH S. TOWER, Baltimore: I wish to ask the authors whether their monkeys showed absence of the threat reaction when a pass was made before their eyes. The bilateral frontal lobectomy preparations of Dr. Hines, which I have had under observation for several years, are not as appreciative of threatening situations as is an ordinary monkey, to the extent that one must be careful with what other monkeys they are placed.

DR. H. A. SHENKIN: Exactly.

DR. B. J. ALPERS: I am interested in the personality changes in general. It is a little difficult to conceive of overactivity as overactivity without some accompanying process.

DR. F. H. LEWEY: In the literature the term "overactivity" is not used in the sense of "hypermotility" in this connection. The word refers exclusively to pacing and does not contain any inference as to the cause of pacing.

DR. H. A. SHENKIN: I think that this interpretation of the term is right.

DR. B. J. ALPERS: This state of overactivity is more than pacing, it is a spread of activity, as I understand it. There is a great deal of activity.

DR. H. A. SHENKIN: All the animals do is pace. There is a personality deficit; they do not react to the presence of visitors as do other monkeys. They show no fear. One can approach them closely before they make any sign of recognition. In the first few weeks they sit gazing off into the distance and pay no attention to anything you may be doing; this is unusual for a monkey, who always has his eyes on you, in one way or another.

Later, instead of reacting in an aggressive fashion, they simply increase the rate of their pacing. The record shows this to occur without the interruption of side actions. They just keep going.

DR. SARAH S. TOWER, Baltimore: Is the region in the human brain corresponding to area 13 ever ablated in removal of the frontal lobe?

DR. H. A. SHENKIN: I doubt it. In man this area would be far back toward the olfactory striae. I doubt whether lobectomy would extend that far.

DR. F. H. LEWEY: One of the interesting points in this presentation is that only bilateral, not unilateral, frontal lobectomy produces pacing. Is there any notable difference in the behavior of persons after unilateral and after bilateral frontal lobectomy for tumor of the brain?

DR. G. D. GAMMON: These reactions were described as pacing reactions; they seem to me to be due partly to the monkey's being confined in a cage. What happens to him if he is turned loose?

DR. H. A. SHENKIN: We have not willingly turned the animals loose. They have escaped on occasion. They will follow the perimeter of the particular confining space that they are in. However, one monkey had a habit of performing a figure eight; only, when he escaped it was a large, instead of a small, figure eight.

Pyramidal and Extrapyramidal Mechanisms in the Cortical Control of Movement.

DR. SARAH S. TOWER, Baltimore.

The cerebral motor cortex has at its command one avenue for direct action on the final motor mechanism, the pyramidal tract, and an indeterminate number of indirect avenues, called in the aggregate the extrapyramidal systems. When the medullary pyramid is severed, the

pyramidal tract alone is interrupted, the extrapyramidal systems being left intact. The functions of the pyramidal tract may then be inferred from the symptoms produced by the lesion, while the functions of the extrapyramidal systems may be studied either in the performance of the intact animal or by electrical stimulation of the cerebral cortex. Studies of this design were carried out on cats, monkeys and chimpanzees and in cases of similar lesions in man collected from the literature. The outstanding results are as follows:

The pyramidal tract has both phasic and tonic functions. Discrete control of movement is the main phasic function. The tonic function reinforces tone and reflexes. A lesion of the pyramidal tract produces characteristically hypertonic paresis, attended in apes and man by the sign of Babinski.

The cortical extrapyramidal systems function both to initiate stereotyped movements or acts and to inhibit tone and movement of skeletal muscles. These various functions are exercised from separate, though overlapping, cortical fields.

Pyramidal and extrapyramidal functions are completely integrated in the totality of cortical motor function.

DISCUSSION

DR. G. P. MCCOUCH: Before discussing Dr. Tower's paper, I wish to express the enthusiasm all feel in the presence of a master in her field who has done a piece of work so thoroughly that no room is left for after-thoughts as to the need of confirmation.

I shall restrict my remarks to the final stage of motor integration. Dr. Tower has spoken of the pyramidal tract as essentially motor, its inhibitory effect being limited to muscles antagonistic to the movement induced. This is precisely the distribution of inhibition that characterizes reflexes of movement. Like the reflex afferent fibers, the corticospinal fibers are now known to terminate dominantly on interneurons, and not, as pictured in the textbooks, on motoneurons. The temptation is strong to assume that reciprocal innervation is mediated solely by the interneurons of the cord and that the corticospinal neurons are purely excitatory. Thus, the entire process could be blocked most readily at the internuncial level. In the case of the flexor response it is precisely at this level that the major share of inhibition by a preceding conditioning stimulus falls.

Of the changes in reflexes, the most radical and puzzling is the Babinski response. I like to think of it as the reversion of function of a two joint muscle, the extensor hallucis longus, from a digital response, under pyramidal control, to flexion of the ankle, under the drive of a spinal reflex.

I fear I am yielding to the temptation to digress into speculation, which Dr. Tower has so meticulously avoided. My excuse is that the primrose path was painted by a penetrating suggestion in one of her own papers.

DR. SARAH S. TOWER: The pyramidal system operates entirely within, one might say, the functional organization of the segmental level. Hence discrete movement and reciprocal inhibition go hand in hand, just as Hering and Sherrington said long ago. But in the cat's motor area, and less conspicuously in the monkey's, after the pyramidal system is cut there is still a tonic inhibitory mechanism, the extrapyramidal, which can be brought into play, and without any following motor act; in this respect it differs from pyramidal inhibition, which can never be dissociated from its corresponding excitation.

DR. G. P. MCCOUCH: In this regard pyramidal inhibition is somewhat analogous to the reflex situation, in that one cannot dissociate the movement from the inhibition.

DR. SARAH S. TOWER: I should put it in this way: The segmental motor mechanism cannot be made to operate other than under its own laws.

DR. G. P. MCCOUCH: So, Dr. Tower, you regard the reciprocal inhibition as essentially spinal?

DR. SARAH S. TOWER: Yes. With respect to the Babinski sign, in the chimpanzee it is outstandingly a mass response. It is difficult to elicit a Babinski response in the chimpanzee without cocontraction of the flexor muscles of the thigh, and sometimes of the long adductor muscles.

I have puzzled a great deal about what really goes into the making of a Babinski response, and I am not sure that I know. There is a great deal of difference between the organization of muscles in the chimpanzee and that in the human being. Dr. McCouch's suggestion perhaps best accounts for it.

There are shifts in emphasis. The effect of pyramidal lesion differs quantitatively with different muscle groups—it is graver for some muscles than for others; that is, the balance of tonic innervation is quite different after pyramidal lesion than it is in the intact animal.

A pyramidal lesion modifies the pattern of excitability of reflexes to a considerable degree; it is not the same in the chimpanzee as it is in the monkey, and it is not the same in the monkey

as it is in the cat. The pyramidal system in the cat operates mostly on the flexor muscles. In the monkey its action is pretty well balanced between the flexor and the extensor groups. In the chimpanzee its influence is on the other side; the extensors, I think, get a little more of it.

DR. G. P. MCCOUCH: Incidentally, is it Dr. Tower's experience that with a sufficiently large ablation one may get the equivalent of a Babinski response in the monkey? The only monkey in which I have seen such an effect was a hemidecerebrate preparation of Fulton's, which showed not a Babinski, but a Chaddock, sign, perhaps the equivalent.

DR. SARAH S. TOWER, Baltimore: I have seen the Babinski response in monkeys, but it is not a reliable sign. There seem to be individual factors in it, actually. In some monkeys the toes turn up and in some they turn down. Apparently, the larger the lesion the greater the tendency to the former reaction.

As for Dr. McCouch's first comment, Dr. Shienkin has already properly put me in my place by showing that there is much more to be said in this field than I have mentioned.

DR. TEMPLE FAY: When Dr. Gammon asked me to discuss this difficult and complex problem, I am sure he meant me to do so from the clinical aspect. What I have to say, therefore, must be mediated in terms of clinical experience. Such an interpretation is limited by those conventional standards to which one has become accustomed, and yet which during the past few years have left one in great confusion with respect to the teachings of the past.

To me the "sign of Babinski," if it is, as Dr. Tower has brought out, a characteristic and persistent sign of section of the pyramidal tract, may offer an important clue to the motor systems from another angle. The sign has been considered by many as more or less a pathologic response, but it is a perfectly normal one in the baby. If one analyzes the movement in terms of segmentation (cortical, as against the lower motor level), and if one interprets Dr. Tower's section of this selective pyramidal system as equivalent to destruction of a motor system which is a comparatively recent addition phylogenetically, then one may see an analogy in the developing responses of the infant. During the early months of life, the free range of paddle movements and defense responses are compatible with the "sign of Babinski," but with control asserted by the development and myelination of the pyramidal tract, the Babinski sign is modified and suppressed, never to appear again unless the pyramidal influence is removed as a result of injury or disease.

I think there is plenty of evolutionary evidence pointing to a mechanism that has been developed out of a free-swimming state and that perhaps the greatest event in the life of the human species is the day of birth, when the infant arrives out of the water stage and becomes a land-breathing animal.

If the big toe is partially rotated outward and away from the digits, as is seen in the frog or the chimpanzee, the movement which is called the Babinski reflex will be seen to be really a fanning or paddle movement of a fin at the fish or amphibian level. When the baby grows up, he loses the Babinski sign, but later, if the pyramidal system is injured, the primitive motor patterns are released and the Babinski sign reappears. Coghill's analysis of movements in *Amblystoma* probably fortifies what Dr. Tower has demonstrated tonight. He found that the pyramidal system in *Amblystoma* developed after the appearance of the tail, head and eye movements. When the appendages appeared, particularly the digits, there was noted the formation of a "new motor system," with fibers that appeared after the original simple segmental pattern had already become established.

Coghill expressed the belief that as more selective movements appeared, an additional motor system developed to meet this need. If one will look at the over-all picture, and view the motor cortex as the site of integrated skilled movements developed for a purpose—all movement had at some time a purposeful meaning—one may get a different concept of the results of destruction at certain levels (i. e., how does the result manifest itself in terms of recent motor pattern controls over primitive reflex patterns and simple swimming movements?).

For instance, animals are tested in various positions—on the back, on the side or sitting—and residual motor responses are analyzed after selective operations. All are familiar with the influence of posture and the Magnus and de Kleijn phenomena. It seems to me that the animal should be placed in the "amphibian position" (on the belly, with the appendages extended to the sides and the thumbs and toes turned toward the head) and immersed in water, if possible, to nullify postural and antigravity effects, as well as to study the effect of operation on the original simple, free-swimming movements at the amphibian level.

I have found that the purposeless, jerking and twisting movements noted in animals during an induced convulsion are converted into an excellent pattern of free-swimming movements when the animal is suspended in water during the attack, with the belly down and the extremities free to assume the amphibian position and paddle function.

I should like to ask Dr. Tower whether she noted any difference after section of the pyramidal fibers between the rotary movements—call them "purposeless" if you like—such as

one can see in cases of acute chorea or of athetosis (extrapyramidal in a clinical sense) and those movements which are of prime flexor-extensor type, such as one sees in a major convulsive seizure.

It seems to me there is evidence of a definite clinical differentiation. Each type of movement is capable of an excitatory mechanism; each is characteristic and at times is free from the other component. Does the pyramidal system, of which 50 per cent of the fibers are of unknown nature, mediate both these phenomena? Or can one say that there is in the pyramidal system per se the better crystallization and objectifying of these rotary movements, of more recent phylogenetic acquisition, into a flexor-extensor pattern of primitive type, with the check modification that she spoke of?

In other words, is function of the pyramidal system divisible into two possible components; control of rotary movements and control of the flexor-extensor system?

I have enjoyed this presentation a great deal, and I am going back to the clinical work at hand with a new interest in Dr. Tower's interpretation of the function of the pyramidal tract.

DR. SARAH S. TOWER, Baltimore: In my work on epileptiform convulsions after section of the pyramidal system I have never seen anything that suggested, or in any way touched on, a choreiform type. But I have seen many reminders of the athetoid type. With my small experience in clinical neurology, I am cautious about getting into this field.

The suggestion that the Babinski response is a swimming derivative is extraordinarily interesting. There has been much speculation about the meaning of the Babinski sign—whether or not it is a primitive reaction. It is my impression that all such extrapyramidal responses come from primitive patterns which are anciently organized in the brain stem. The suggestion that the Babinski sign is part of a swimming mechanism is in this vein.

DR. B. J. ALPERS: Have any of the animals shown edema?

DR. SARAH S. TOWER: No, I have never seen it, although I have looked for it.

DR. F. H. LEWEY: Dr. Tower stated that the pyramidal tracts reenforce the segmental reflexes. In other words, loss of impulses over the pyramidal tracts should decrease the segmental reflexes. This, of course, is contrary to what one has learned previously. It used to be taught that the higher motor centers braked the subordinated motor levels and that the segmental reflexes were most exaggerated when freed from any regulation by higher centers. Probably this is one of the errors which one must rectify now.

What motor function survives when the whole cortex is out of commission except for the anterior central convolution?

What is known about the integration of pyramidal and extrapyramidal function in the final movement?

DR. SARAH S. TOWER, Baltimore. I would remind you of the effect of ordinary hemiplegia on the superficial reflexes, the abdominal and cremasteric reflexes, which are dereinforced, if one may say so. With a pyramidal lesion, the abdominal reflex disappears in all primates. In the monkey the cremasteric reflex also disappears. None of my chimpanzees were males, so I know this only for the monkey.

In ordinary hemiplegia in man, loss of pyramidal reenforcement of the segmental reflexes appears only in those which do not involve the antigravity mechanism. This mechanism is under release because of the associated extrapyramidal lesion, which Dr. Hines worked on extensively, in consequence of which these reflexes are exaggerated or spastic. But the abdominal and cremasteric reflexes are not of this nature and show the pyramidal depression, not the extrapyramidal release.

I believe that the final integration takes place in the internuncial and final motor mechanism of the cord. That, at least, would represent the final level of integration. In a normally functioning animal or human being there is, I presume, a tremendous amount of initial integration in the complex organization of the cerebral cortex, but that has not come under my survey at all in these experiments. Bard, in his cats with remnants of the frontal pole, tried to approximate a preparation in which a portion of the cortex exerts control over the pyramidal tract alone, but actually one cannot even approximate it because the field which gives origin to the pyramidal system also gives rise to numerous extrapyramidal systems. Moreover, for practical purposes, the extrapyramidal systems must be defined as including the prespinal collaterals of the pyramidal system because one cannot at present separate, for example, a corticonigral collateral of a pyramidal tract fiber from an independent corticonigral fiber. Until that can be done, all must be lumped together. Hence one could not possibly have a portion of the cortex controlling the pyramidal system, with the extrapyramidal systems thrown out.

DR. G. P. MCCOUCH: In support of Dr. Tower's contention—not that it needs support—that there is a tonic reenforcement of the central excitatory state from the pyramidal system, the following observation appears pertinent: If one excises area 4, allows the animal to recover

from the immediate effects of the operation and then transects the cord, there is an earlier recovery of reflexes on the side of the previous deprivation, the previously parietic side, than on the previously intact side, which suffered its entire spinal shock at the second stage. I realize that such an experiment is open to the criticism that area 4 contains extrapyramidal, as well as pyramidal, elements. I should be interested to see such an experiment repeated with section of the pyramidal tract rather than with ablation of area 4.

DR. MICHAEL SCOTT: I should like to ask Dr. Tower whether there is any clinical similarity between section of the pyramid as she made it and section of the pyramidal tract in the high cervical region.

DR. SARAH S. TOWER, Baltimore: All my animals with experimental sections in the cord have had at least some of the elements of spasticity, which is not true of those with section of the pyramid. A student of Dr. Hines, working on that problem, was able, by careful section of the cord, to get some preparations in which the spasticity was much more pronounced than in others.

As the pyramidal tract passes through the decussation and into the cord, it mingles with the lateral reticulospinal tract, overlaps the rubrospinal tract and plunges into the general proprius field of the spinal cord itself. Lesions of the cord are, therefore, inevitably mixed, and I presume the element of spasticity enters with this mixture. It is the chief difference between the results of section at the two levels.

Loss of discrete movement is, of course, characteristic of all lesions of the pyramidal tract, regardless of level. This is the common feature.

PHILADELPHIA PSYCHIATRIC SOCIETY

ARTHUR P. NOYES, M.D., *in the Chair*

Regular Meeting, Nov. 13, 1942

Symposium: Complications of and Contraindications to Electric Shock Therapy.

DR. THEODORE L. DEHNE: In the past two years my associates and I have treated about 120 patients at Friends Hospital. These patients represent a wide field of mental illnesses, many of which were treated semiexperimentally. In brief, we have come to the conclusion that electric shock therapy is most useful with agitated depressions, fairly useful with simple depressions and rather disappointing with manic reactions. A number of schizophrenic patients were given this therapy as a palliative rather than as a curative measure. Nearly all such patients became quieter and were more easily cared for. Early in our experience we hesitated to treat physically impaired patients, for a variety of reasons; as time passed, however, we concluded that many patients who exhibited what we believed to be disabilities contraindicating the induction of convulsions deserved such treatment because of the gravity of their mental illness.

Contraindications referable to the skeletal system included recent fractures and arthritic changes, particularly those of osteoarthritic type. However, several patients with severe arthritis were treated without damage. Of 120 patients, however, 5 suffered compression fractures in the thoracic region and 1 a fractured humerus, only the latter being considered serious.

Cardiac contraindications usually included arteriosclerosis, hypertension and cardiac enlargement due to any cause. However, several patients with advanced arteriosclerosis and 1 with pronounced enlargement of the heart with auricular fibrillation received the therapy without noticeable damage.

Pulmonary contraindications did not have to be considered in this series. Diseases of the central nervous system, particularly degenerative changes due to arteriosclerosis or senility, were considered contraindications, but patients with both types were treated with electric shock without apparent acceleration of damage to the central nervous system. One highly excited patient with dementia paralytica was given the therapy, after which he was somewhat quieter and easier to care for.

No deaths were directly attributed to electric shock. However, a highly excited alcohol addict with arteriosclerosis and organic heart disease had a stroke twenty-six hours after a treatment; he died subsequently.

In summary, we believe electric shock is a relatively safe procedure and that the reasons for its use should be dictated by the best results that may be accomplished.

DR. HOWARD K. PETRY, Harrisburg, Pa.: Electric shock treatments were first given at the Harrisburg State Hospital in February 1941. To date my colleagues and I have completed treatment in 148 cases.

Complications.—Skeletal System: Bilateral dislocation of the mandible occurred in 3 cases; pain and swelling of the right knee, in 3 cases; pain in the gastrocnemius muscle of the right leg, in 1 case, and pain in the back, in 6 cases.

Cardiovascular System: Vascular collapse, resulting in discontinuation of treatment, occurred in 1 case, and edema of the ankles due to cardiac decompensation, in 1 case.

Respiratory System: Prolonged apnea appeared in 3 cases.

Central Nervous System: An epileptiform convulsion, thirty-two days after the last treatment, occurred in 1 case; marked confusion, necessitating discontinuation of treatment, was present in 1 case, and manic excitement in a previously depressed patient, necessitating discontinuation of treatment, was noted in 1 case.

Muscular System: Ventral hernia and abdominal pain, with discontinuation of treatment, occurred in 1 case.

Miscellaneous Complications: Two conjunctival hemorrhages, both in the same case, were encountered.

No deaths occurred as a result of the treatment.

Contraindications were active or latent pulmonary tuberculosis, severe arthritis with deformity, poor cardiac tolerance to exercise and severe inanition.

The data on the results of therapy are analyzed in the following tabulation.

Psychosis	Total No. of Cases	Recovery	Improve- ment	No Improvement
Manic-depressive	43	25	12	6
Manic phase.....	6	2	1	3
Depressed phase.....	37	23	11	3
Involutional melancholia.....	34	19	5	10
Schizophrenia	60	7	12	41
Simple	12	1	4	7
Hebephrenic	3	..	2	1
Catatonic	20	3	4	13
Paranoid	25	3	5	17
Psychoneurosis	5	2	2	1
Unclassified	6	1	1	4
Total number.....	148	54	32	62
Percentage of cases.....	100	36.5	21.6	41.8

Average Duration of Illness

Psychosis	Recovery	Improvement	No Improvement
Manic-depressive	1 yr. 1½ mo.	4 yr. 3 mo.	9 yr. 10½ mo.
Involutional melancholia.....	1 yr. 3 mo.	2 yr.	2 yr. 10 mo.
Psychoneurosis	4 mo.	6 yr.	5 mo.
Schizophrenia	5.5 mo.	2 yr. 8 mo.	3 yr. 10 mo.
Unclassified	2.6 yr.	1.5 yr.	8.7 yr.

Average Age

Psychosis	Recovery	Improvement	No Improvement
Manic-depressive	44.2 yr.	50.7 yr.	43.6 yr.
Involutional melancholia.....	55 yr.	53.2 yr.	55.7 yr.
Psychoneurosis	34.5 yr.	36.5 yr.	33 yr.
Schizophrenia	27 yr.	30.6 yr.	30.9 yr.
Unclassified	47 yr.	51 yr.	46 yr.

DR. ARTHUR LINDENFELD, Allentown, Pa. (by invitation): Electric shock treatment was carried out at the Allentown State Hospital in 55 cases, representing various psychiatric diagnoses. In all cases roentgenographic and electrocardiographic studies were made before, at times during and at the conclusion of treatment. The following complications and contraindications were observed:

Skeletal System.—Advanced arthritic changes of the spine were noted in 2 cases. There were no fractures or dislocations.

Cardiovascular System.—In 2 cases treatment was refused, in 1 of which coronary disease, and in the other chronic rheumatic valvular heart disease with fibrillation, was present. In 2 cases treatment was discontinued, in 1 of which auricular flutter, and in the other persistent hypertension, with a blood pressure of 200 systolic and 120 diastolic, and peripheral sclerosis.

developed. In 1 case fibrillation was treated successfully. In 1 case with coupling and in another with auricular premature contractions therapy is being carried out, without complications thus far.

Respiratory System.—Treatment was refused in a case in which questionable tuberculous activity was present.

Central Nervous System.—In 1 case therapy was refused because of a history of convulsions earlier in life and electroencephalographic evidence of epilepsy.

No deaths occurred which were directly attributable to electric shock therapy. In 2 cases the patients committed suicide after treatment was discontinued, before they had shown satisfactory improvement.

DR. GRANVILLE L. JONES, Marlboro, N. J. (by invitation): At the New Jersey State Hospital, since Feb. 16, 1941, my associates and I have given electric shock treatments in a total of 508 cases. We have employed electric shock alone, electric shock combined with insulin, electric shock combined with curare and electric shock combined with insulin and curare.

We have no fixed contraindications. We consider each case on its merits, balancing the probability of improvement against the type or severity of the possible complications.

We had 16 cases of dislocation of the jaw and 1 case of subacromial bursitis. These complications were trivial. We had 1 case of subluxation of a cervical vertebra, with no serious results. We discovered 9 compression fractures of the thoracic vertebrae, resulting in nothing more than slight kyphosis. We take roentgenograms of the spines of all candidates, and any with pathologic conditions which reduce the flexibility of the spine or the density of the bone, such as severe hypertrophic or atrophic changes or previous injury or disease, are not considered suitable for treatment. We have sometimes used curare with such patients, as well as with a few who had suffered fractures during treatment. A patient aged 50 who had been psychotic for thirty-six years had a fracture of the humerus. Our results are in accordance with the observation of Graves and Pignataro that the incidence of fracture during metrazol shock depends more on the duration of the psychosis than on the age of the patient.

We had 1 case of pulmonary edema and 6 cases of circulatory collapse, the latter being probably of central origin. The symptoms were imperceptible pulse, apnea or respiratory distress and deepening cyanosis, changing to pallor. I know of no way in which to predict such a reaction; hence I am not certain that the cardiovascular contraindications have any bearing on it. We do not treat patients with past or present cardiac decompensation or disease of the coronary arteries or with arrhythmia that is demonstrably a symptom of organic disease. We have induced electric shock in patients with moderate arteriosclerosis, with moderate hypertension and with old rheumatic heart disease, and in the case of a patient with thrombophlebitis we combined electric shock therapy with curare. When tachycardia or arrhythmia appears, treatment is promptly discontinued. We do not take electrocardiograms except in doubtful cases or when symptoms arise.

Aside from disturbances of memory, which are almost always transitory, our only complication referable to the central nervous system has been prolonged or delayed convulsions, with no serious sequelae. A contraindication is any localized organic disease of the brain. Generalized disease of the brain, such as senility, arteriosclerosis without focal signs or even dementia paralytica, is not considered a contraindication if there are urgent psychiatric indications, such as severe agitated depression or exhausting excitement. We have treated a patient with Huntington's chorea and a few children with postencephalitic behavior disorders.

We have had no cases of tuberculosis, pneumonia or pulmonary abscess as a result of electric shock therapy. A case of pulmonary embolism will be discussed in connection with deaths associated with the therapy. We usually regard active tuberculosis as a definite contraindication to any form of shock therapy, but we treated a patient who had an active lesion, without spread of the disease. Inactive tuberculosis is not a contraindication. In 2 cases an acute infection of the respiratory tract developed during treatment. We suspend therapy under such circumstances, as well as when fever develops from any cause. In all cases roentgenograms of the chest are made before treatment, and for cause during and after therapy.

Other diseases observed were parotitis, in 1 case, and disseminated lupus erythematosus, in 1 case.

In 3 cases death followed exhaustion from psychotic excitement one, two and three days respectively after a single electric shock. In these cases death was probably not even hastened by the shock therapy, which was a desperate effort to terminate the severe and ominous exhaustion. In 1 case death resulted from an intravenous injection of magnesium sulfate, given for the curarization effect. In another case death was from pulmonary embolism, apparently as a result of infectious phlebitis, which complicated bilateral otitis media one week after the last shock treatment. Electric shock is probably contraindicated in cases of chronic disease of the middle ear, certainly when there is active infection.

A woman aged 23, with a psychosis diagnosed as manic-depressive insanity, perplexed type, had the cutaneous symptoms of lupus erythematosus on admission, which was not recognized as the disseminated form. She was given ten insulin and six electric shock treatments. Pleurisy developed, and treatment was discontinued. The shocks may have played some part in her death, which, however, did not occur until two months after the last treatment.

DR. HERBERT HERSKOVITZ, Norristown, Pa.: Since April 1940 174 patients have received electric shock therapy at the Norristown State Hospital. Two had fracture of a midthoracic vertebra and 4 dislocation of the jaw. The latter was reduced with no difficulty. There were no deaths or cardiac, pulmonary or other complications, except for memory defect. This defect, which has not been stressed by the previous speakers, I find to be rather general and often prominent. Therefore, patients whose occupation requires intellectual ability are selected for treatment with caution.

Prior to treatment each patient receives a thorough physical examination; in addition to the usual studies of the blood and urine, roentgenograms of the chest and spine and an electrocardiogram are taken. Until recently a roentgenogram of the spine has been taken after treatment.

The criteria for and contraindications to treatment include heart disease of any type; arteriosclerosis, either cerebral or generalized; hypertension; previous cerebral vascular accidents; any acute disease of the respiratory tract; previous fractures which have not healed firmly, and hernia. Healed tuberculous lesions, unless extremely small, are considered a contraindication to treatment. As a rule, patients over 60 years of age are not treated by this method. When an exception is made, the patient is studied thoroughly and treatment proceeds with caution. Prior to each session the patient's temperature and blood pressure are taken, and if either is elevated treatment is withheld. Emaciation is not considered a contraindication.

It is believed that the conservatism used in selection of patients for treatment explains the low incidence of complications at this institution. As the previous speakers have indicated, the course of the illness frequently determines whether or not the patient shall receive treatment. Electric shock therapy is of value for depressive psychoses, particularly involutional melancholia, but is of little value for schizophrenia.

DR. JOHN H. TAYLOR JR, Trenton, N. J. (by invitation): Since October 1940 my associates and I have employed electric shock therapy in 1,133 cases, in 448 of which electric shock was combined with insulin. In the remaining 685 cases electric shock therapy was used alone.

Complications.—These included loosening of teeth, in 22 cases; dislocation of the jaw, in 12 cases; dislocation of the shoulder, in 4 cases; fracture of the neck of the humerus, in 2 cases, and fracture of the head of both humeri, in 1 case.

There were 6 cases of compressed fracture in the thoracic region, with slight lateral displacement in 1 case. The fourth, fifth, sixth, seventh and eleventh vertebrae were involved in 1 case each, and the fifth and sixth vertebrae, in 1 case. In none of these cases were any neurologic symptoms evident, nor was any treatment other than supportive strapping employed; there apparently were no after-effects. Transverse fracture of the neck of the femur occurred in 3 cases.

We did not note any cardiac or pulmonary complications other than the expected reactions during treatment, or any complication referable to the central nervous system.

In several cases periods of forgetfulness and confusion developed, which lasted from two or three days to six months, the longer period being exceptional. The confusion, however, cleared up in all cases, and to date we have not noted any permanent mental impairment.

Types of Psychoses Treated.—We treated all types of functional psychoses, as well as epilepsy and psychosis with syphilitic meningoencephalitis. When we first began to use electric shock therapy, we treated manic-depressive psychosis, involutional psychosis and catatonic schizophrenia by this method alone. We found that the patients made spectacular improvement but that the improvement was not sustained. We now do not use electric shock therapy alone with any acute functional psychosis, but combine it with insulin shock. The combination of the two treatments has given more frequent and better sustained improvement than either treatment alone. We now use electric shock for patients with chronic disturbances or epilepsy and for disturbed patients with dementia paralytica. However, we emphasize that in our experience insulin therapy is the treatment of choice, and in the management of schizophrenia we use electric shock only as an adjuvant when the patient does not respond to insulin shock alone.

With the acute manic-depressive states, catatonia and involutional psychosis of the depressed, agitated type, we frequently start the insulin and the electric shock therapy simultaneously but continue the insulin shock treatment after the completion of a course of fifteen convulsions.

We have treated 22 patients with psychoses accompanying syphilitic meningoencephalitis who were admitted to the hospital in an excited and disturbed state. These patients all responded rapidly and within a few days made a good hospital adjustment. They were then given fever therapy.

Epilepsy: The Trenton State Hospital does not treat epileptic patients, as New Jersey has an epileptic colony at Skillman. However, a few patients who were subject to violent furors and showed homicidal tendencies are in residence at the Trenton State Hospital, for custodial reasons. Six patients were given a course of fifteen convulsions induced by electric shock, after which therapy was continued with one or two treatments a week for an indefinite period. These patients all showed improvement in their hospital adjustment; the frequency of their convulsions was diminished, and the periods of excitement entirely disappeared in most cases.

One case is interesting. A white man aged 42, who had been subject to epileptic seizures for thirty years, was admitted to the hospital in 1938; he was subject to seizures approximately every other day until Sept. 2, 1941, when he had 5 seizures. On September 3 he had 5 seizures; on September 4, 2 seizures; on September 5, 8 seizures; on September 6, 10 seizures; on September 7, 3 seizures; on September 8, 13 seizures; on September 9, 11 seizures; on September 10, 7 seizures, and on September 11, 12 seizures. On that date he was given his first electric shock treatment. The following day he had 10 seizures, and another electric shock treatment was given. On September 13 he had 1 seizure, and from that date until Jan. 11, 1942, a period of four months, he had no seizures. On January 11 he had a seizure, and another course of electric shock was started. He remained free from convulsions until Feb. 2, 1942; at this time, at his request, his family withdrew permission for treatment. Since that date he has continued to have convulsions approximately every other day, but there has been no return of his repeated convulsions.

Chronic Psychoses: By far the largest number of patients to receive electric shock therapy alone were the dirty, denuded, deteriorated and disturbed schizophrenic patients. These patients made a remarkable change in their institutional adjustment, and the majority improved to the point of remaining clothed, going to the cafeteria and working in occupational therapy groups in the wards. We found, however, that if the treatments were discontinued the patients soon returned to their previous level; therefore we maintain these patients on a regimen of one or two treatments a week for an indefinite period.

Curare.—We did not employ curare with our patients receiving electric shock therapy, but used it with 32 patients whom we treated with metrazol. We discontinued its use because in order to secure what we considered sufficient benefit from the drug, it was necessary to give large doses; in several instances respiratory paralysis developed, and artificial respiration had to be given for several hours.

Contraindications.—Our contraindications to treatment at present are cardiac decompensation, active pulmonary tuberculosis, hypertension, bony changes in the spine and hernias.

DR. THOMAS H. WRIGHT JR.: Four hundred patients at the Pennsylvania Hospital for Nervous and Mental Diseases were treated with electric shock. Curare was used routinely.

Skeletal System.—Dislocation of the left humerus occurred in 1 case. No contraindications referable to the skeleton were noted.

Cardiovascular System.—Complications were coronary thrombosis, in 1 case; auricular fibrillation, in 2 cases, and vasomotor collapse, in 2 cases.

A contraindication was severe cardiovascular disease.

Respiratory System.—Complications were severe apnea; rupture of a small pulmonary blood vessel, with recovery, in 1 case, and surgical shock, in a case of therapeutic pneumothorax.

A contraindication was severe active disease of the respiratory tract.

Central Nervous System.—A complication in 1 case was a generalized spastic state, which lasted for four days, with spontaneous recovery.

A contraindication was organic disease of the central nervous system.

Death occurred in 1 case, that of a man aged 50 years. A mild convulsion occurred during the first two minutes; breathing was satisfactory, then became irregular and stopped. The pulse continued to be good, but finally stopped. Permission for autopsy was refused.

Conclusion.—Contraindications center around severe organic illness. Even under such circumstances, however, the severity of the mental illness should be taken into consideration when one is trying to judge whether electric shock should be given.

DR. C. A. ZELLER: At the Philadelphia State Hospital 155 patients, the majority of whom had chronic schizophrenia, were treated. No fracture or orthopedic complication was noted. There were 12 dislocations of the jaw, 6 occurring in the same patient, in spite of prophylactic measures. A man of 48 presented split heart sounds, which returned to normal after suspension of treatment. A woman aged 55 died of bronchopneumonia two months after the completion

of several series of shocks, totaling sixty-two treatments (Alpers, B. J., and Hughes, J.: *J. Neuropath. & Exper. Neurol.* **1**:173 [April] 1942). Contraindications are an age of 60 or over, arteriosclerosis, hypertension, tuberculosis in any stage or location, cardiac disease of any type, any disease of bone and advanced inanition.

DISCUSSION ON PAPERS PRESENTED IN THE SYMPOSIUM ON ELECTRIC SHOCK THERAPY

DR. LAUREN H. SMITH: Electric shock therapy is proving effective in treatment of involutional melancholia and manic-depressive psychosis. At the Pennsylvania Hospital immediate recovery occurred in 70 per cent of patients with involutional melancholia, in 59 per cent of patients with manic-depressive psychosis, depressed phase, and in 56 per cent of patients with manic-depressive psychosis, manic phase. Manic patients did not maintain their recovery, and frequent relapse occurred. Electric shock therapy was not effective with schizophrenia, the rate of recovery not exceeding the rate of spontaneous recovery. Results in treatment of the psychoneuroses were likewise disappointing.

The complications arising in this type of therapy have been adequately covered in the various papers presented this evening. These range from fractures and dislocations to complications involving the cardiovascular and respiratory systems, memory defects and even death. While from a statistical viewpoint these complications occur in only a small percentage of patients treated, they impose, nevertheless, the responsibility on the physician of considering with care the question of electric shock treatment.

Contraindications to electric shock therapy are a matter of opinion. Each patient should be considered individually, the advantages to be gained by possible psychiatric recovery always being balanced against the possible risks of the therapy.

DR. JOHN H. STAUFFER: At the Philadelphia General Hospital, my associates and I have so far treated 454 patients. One patient died, a man aged 70, who had gradually been growing worse for six years. He complained of loss of appetite and vague pains, became increasingly depressed and self accusatory, wanted to die and had to be fed with a tube. Physical examination showed mild electrocardiographic changes, due to arteriosclerosis. He was given four electric shock treatments combined with curare; during the fifth treatment he became dyspneic and died thirty-six hours later.

One man had fracture of the acetabulum, and another, aged 59, had abdominal hernia. A woman aged 47 had six successive convulsions after the first treatment. It was believed that she had had encephalitis a year prior to the treatment. There were several instances of hemorrhage of the conjunctiva and dislocation of the jaw and a few fractures of the vertebrae. One depressed patient with dementia paralytica, who had been treated with malaria with no improvement, was given electric shock therapy and is now back on the police force. We treated another patient with the same disease, who did not recover.

In certain cases we have induced subshock. One woman aged 72, with diabetes, made a good recovery under such treatment.

Shock apparently induces the malnourished patient to eat, and he gains in weight and strength.

In my opinion, if the patient's heart is in good condition it is safe to try electric shock therapy.

CORRECTION

In the article by Drs. Arnold M. Meirowsky and Feori F. Pipito entitled "Surgical History of Trigeminal Neuralgia," in the April issue (*ARCH. NEUROL. & PSYCHIAT.* **49**:574, 1943), references to two articles by Drs. Grant and Weinberger were unintentionally overlooked. The new sentence beginning at the end of the seventh line of the last paragraph on page 579 should read: "Grant and Weinberger and Olivecrona³⁹ have already suggested . . .," and reference 39 should read: "Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: I. Relief of Facial Pain and Summary of Operative Results, *Arch. Surg.* **42**:681 (April) 1941; Experiences with Intramedullary Tractotomy: IV. Surgery of the Brain Stem and Its Operative Complications, *Surg., Gynec. & Obst.* **72**:747 (April) 1941. Olivecrona, H.: Tractotomy for Relief of Trigeminal Neuralgia, *ARCH. NEUROL. & PSYCHIAT.* **47**:544 (April) 1942."

Book Reviews

Autonomic Regulation. By Ernst Gellhorn. Price \$5.50. Pp. 373, with index and bibliography. New York: Interscience Publishers, 1942.

The text is divided into five parts: (1) a general introduction; (2) autonomic reactions, involving primarily the respiratory and circulatory systems; (3) autonomic-endocrine integration; (4) autonomic-somatic integration, and (5) results and applications.

In his introduction, the author states that any understanding of the physiology of the mammalian organism must obviously take into consideration the mutual relationship of the various organs and determine how any change in the external environment affects the organs of the body. This consideration of the interrelationship of organ systems in environmental adjustment the author calls the "organismic principle." The central nervous system is involved in all these conditions.

The autonomic nervous system, by altering the circulation, respiration, heat production, heat loss, changes in blood volume and erythrocyte count, protects the cortex of the brain in a most effective manner from harmful alterations in the internal environment.

The author states that the book is an experimental survey in which he attempts to analyze the function of the organism under a variety of conditions. He states that under stress and strain there have been developed during the stages of phylogenetic evolution a set of reactions which retain the purposeful functions of the organism. The discovery of these principles becomes the task of an organismically oriented physiology; the application, the problem of a scientifically oriented medicine and psychology.

An attempt is made to understand the physiologic basis of the fact that it is the autonomic, and not the somatic, system that is responsible for the regulation of various adjustment reactions of body organs. It is pointed out that the autonomic nervous system differs fundamentally from the somatic centers inasmuch as changes in the internal environment which lead to a depression of the cerebrospinal system are accompanied by an increased excitability of the vegetative centers. These observations lead to a discussion of the mutual relation of the autonomic and the somatic nervous system. They show that the autonomic nervous system is not only an efferent system, carrying impulses from the somatic system to the various visceral organs, but an afferent system, the impulses of which significantly alter the excitability of the somatic system. This is illustrated not only for physiologic but for pathologic conditions, such as convulsions.

The autonomic reactions to hypercapnia, anoxia, asphyxia, hypoglycemia and hemorrhage are carefully considered and not only serve as examples of physiologic adjustment reactions, but throw important light on pathologic processes. An attempt is made to utilize these observations in the problems of neuropsychiatry. It is shown that the reactivity of the autonomic centers of schizophrenic patients is fundamentally different from that of normal persons. In the light of these observations, the physiologic effects of insulin, of hypoglycemia and of convulsions, induced either by drugs or by electric current, are studied, and a physiologic theory of the treatment of schizophrenia is presented.

Starting from a rather short consideration of the anatomic and physiologic foundations of the autonomic nervous system, the author proceeds carefully and methodically to expand his discussion, as already outlined, by a consideration of his own investigations and a review of the literature. His consideration of the literature is exhaustive, the bibliographic index listing 1,100 titles. One gets the feeling throughout that the author knows just what he is building, and as he fits fragments of evidence together, the shape of the structure becomes apparent.

Dr. Gellhorn states clearly that his mechanistic consideration of human reactions and emotions is not complete; whether or not one agrees with his attempt, it is apparent that his presentation of the problem is admirable. The point will eventually be reached at which all physicians will see that the consideration of psychic and somatovisceral factors in the production of human emotional responses is not a state in which the acceptance of one point of view demands a rejection of the other. It is perhaps merely a question of the emphasis on one or the other factor, both factors being constantly in action. This book may play a valuable part in guiding neuropsychiatrists toward such a point of view. This volume is recommended and should be a part of every one's neurophysiologic library.

ELECTROENCEPHALOGRAPHIC FOCI ASSOCIATED WITH EPILEPSY

ERNA L. GIBBS

H. HOUSTON MERRITT, M.D.

AND

FREDERIC A. GIBBS, M.D.

BOSTON

One of the chief clinical assets of electroencephalography is its power to localize gross cortical lesions. The early work of Berger¹ and of Foerster and Altenburger² called attention to the possibilities of the method, but the practical value of electroencephalography for the localization of gross lesions prior to operation was first clearly demonstrated by Walter.³ The closely related problem of localization of a discharging lesion or seizure focus was the subject of early reports by Jasper⁴ and by Gibbs, Lennox and Gibbs⁵ and of later reports by Jasper and Hawke⁶ and by Casamajor and his co-workers.⁷ Reviews of the literature on electroencephalographic localization and lengthy bibliographies have been published elsewhere.⁸

As a result of their studies, Jasper and his associates⁹ concluded that the most important characteristics of a seizure discharge are the degree and direction

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From the Department of Neurology, Harvard Medical School, and the Neurological Unit, Boston City Hospital.

1. Berger, H.: Ueber das Elektrenkephalogramm des Menschen, *Arch. f. Psychiat.* **87**: 527-570, 1929; *J. f. Psychol. u. Neurol.* **40**:160-179, 1930; *Arch. f. Psychiat.* **94**:16-60, 1931; **98**:231-254, 1932.

2. Foerster, O., and Altenburger, H.: Elektrobiologische Vorgänge an der menschlichen Hirnrinde, *Deutsche Ztschr. f. Nervenhe.* **135**:277-288, 1935.

3. Walter, W. G.: The Location of Cerebral Tumors by Electroencephalography, *Lancet* **2**:305-308, 1936; Electro-Encephalogram in Cases of Cerebral Tumour, *Proc. Roy. Soc. Med.* **30**:579-598, 1937.

4. Jasper, H. H.: Localized Analyses of the Function of the Human Brain by the Electroencephalogram, *Arch. Neurol. & Psychiat.* **36**:1131-1134 (Nov.) 1936.

5. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, *Arch. Neurol. & Psychiat.* **36**:1225-1235 (Dec.) 1936; Localizable Features of the Electrical Activity of the Brain in Petit Mal Epilepsy, *Am. J. Physiol.* **116**:61, 1936.

6. Jasper, H. H., and Hawke, W. A.: Electro-Encephalography: IV. Localization of Seizure Waves in Epilepsy, *Arch. Neurol. & Psychiat.* **39**:885-901 (May) 1938.

7. Casamajor, L.; Smith, J. R.; Constable, K., and Walter, C. W. P.: The Electroencephalogram of Children with Focal Convulsive Seizures, *Arch. Neurol. & Psychiat.* **45**: 834-847 (May) 1941.

8. (a) Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941, p. 221. (b) Jasper, H. H.: Electroencephalography, in Penfield, W., and Erickson, L. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, chap. 14, pp. 380-454.

9. Jasper, H., and Kershman, J.: Electroencephalographic Classification of the Epilepsies, *Arch. Neurol. & Psychiat.* **45**:903-943 (June) 1941. Jasper.^{8b}

of spread. Jasper proposed that seizure discharges be classified into the following three categories: localized, bilaterally synchronous and diffuse. We agree that for certain purposes such classification has advantages. There are important correlations between spread, wave form, etiologic factors and clinical symptoms. The problem of diagnosis and treatment of epilepsy often centers on the question of whether or not localizing signs are present. Electroencephalographic evidence of a focus of abnormal activity is an important localizing sign. As will be shown, however, certain types of waves are more significant than others. In a complete electroencephalographic classification¹⁰ it seems wise to consider not only the degree and type of spread but also the frequency and wave form.

MATERIAL

In 174 cases (15 per cent) of a total series of 1,161 cases of epilepsy studied at the Boston City Hospital between 1938 and 1942, either localizing symptoms or signs were observed on neurologic examination or an electroencephalographic focus was found. It is with these 174 cases that the present report is chiefly concerned. The presumed "cause" of seizures in these

TABLE 1.—Incidence of Focal Clinical Signs or Symptoms Among Cases With and Without Electroencephalographic Foci

Type of Electroencephalographic Focal Disorder *	Number of Cases	Cases with Focal Seizures or Localizing Clinical Signs †	
		Number	Percentage
1/4 to 2 per sec. (slow 3).....	46	35	76
18 to 22 per sec. (fast 2).....	11	7	64
Spikes.....	45	24	53
Petit mal variant.....	19	10	53
3 to 6 per sec. (slow 2).....	22	10	45
Petit mal.....	14	3	21
Low amplitude.....	1	1	..
Psychomotor.....	2	2	..
Total number with electroencephalographic focus.....	160	92	58
Total number without electroencephalographic focus..	1,001	14	1
Total number of cases of epilepsy.....	1,161	106	9

* The meaning of the terms used in parentheses in this table, and in table 2, is explained in the legend to figure 10.

† In every case with an electroencephalographic focus and clinical localizing signs or symptoms, the site of the electroencephalographic focus was in agreement with the clinical localization.

cases was as follows: trauma, in 69 cases; infection, in 20 cases; vascular disease, in 14 cases; birth injury, in 12 cases, and developmental defects, in 4 cases. In 55 cases there was no evident cause for the seizures. Cases of brain tumor were not included because it was believed that such cases can be considered more profitably as a separate group. Special attention is given in the present report to the 160 cases in which electroencephalographic foci were present, and these cases are compared with the 14 cases in which clinical localizing signs or symptoms existed but no electroencephalographic focus was noted.

METHOD

The electrical activity of the left and right frontal, parietal and occipital cortex was recorded with a Grass six channel electroencephalograph. In some cases the activity of the temporal cortex was recorded also. All records were made with monopolar leads, the indifferent electrode being formed by interconnecting the two ear lobes. Monopolar leads were used because such leads, with six channel recording, gave the most comprehensive and easily interpreted record of both normal and abnormal activity. After long trial with both monopolar and bipolar leads, we found that with six channel recording it is possible to localize abnormalities and differences in activity between homologous areas at least as accurately with monopolar as with bipolar leads. In our experience, monopolar localization

10. Gibbs, E. L.; Gibbs, F. A., and Lennox, W. G.: Electroencephalographic Classification of Epileptics and Controls, Arch. Neurol. & Psychiat., to be published.

(with a six channel instrument) was simpler and slightly more reliable than bipolar localization. Cortical disorder was considered focal only when it was consistently localizable to a given area. The general procedure and the type of electrode employed have been described elsewhere.^{8a} Patients were studied during their interseizure periods. Cortical activity was recorded for fifteen minutes; two minutes was allowed for overventilation and three minutes for recovery.

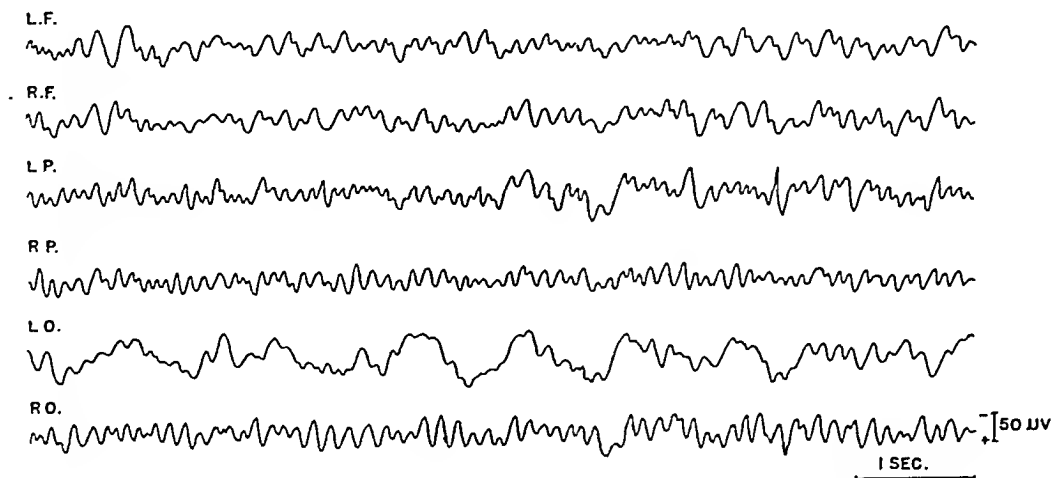


Fig. 1.—Focus of irregular $\frac{1}{2}$ to 2 per second activity in the left occipital and parietal areas of a man aged 54. One year ago there occurred transient right hemiplegia and aphasia due to cerebral thrombosis, probably on the basis of cerebral arteriosclerosis. Generalized convulsive seizures began nine months ago. No localizing neurologic signs were present at the time the record was taken.

In this, and in figures 2 to 10, letters at the left indicate the left and right frontal, parietal and occipital leads. In the lower right corner are shown the deflection produced by 50 microvolts and a time calibration of one second.

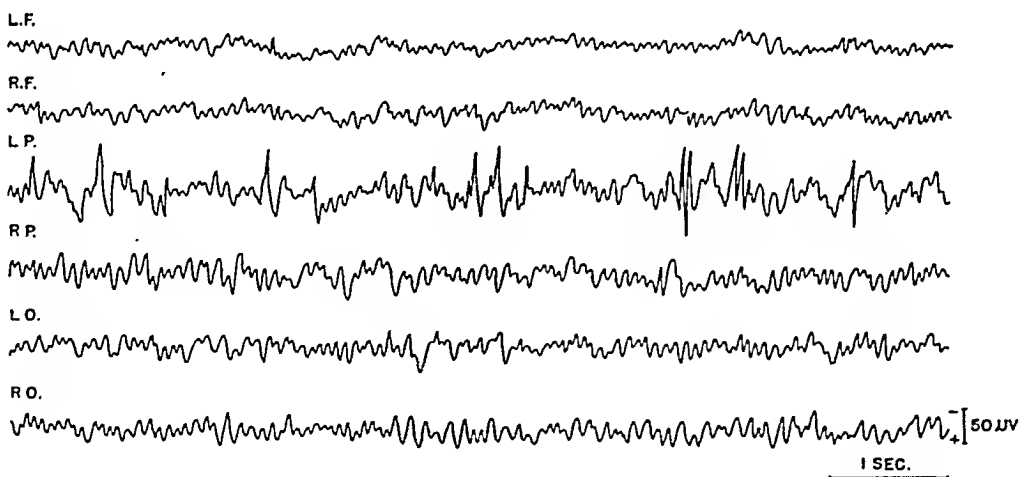


Fig. 2.—Focus of spike activity in the left parietal area of a girl aged 11. Birth was by forceps delivery, with considerable facial disfigurement. Convulsions involving the right side had occurred for the past two years. No focal neurologic signs were noted.

RESULTS

The 174 cases with either localizing symptoms or signs on neurologic examination or an electroencephalographic focus fell into the following group: 14 cases with clinical localizing signs but without any electroencephalographic focus; 68 cases with an electroencephalographic focus but without any symptoms indicating a localized lesion, and 92 cases with an electroencephalographic focus and symptoms or signs pointing to a localized lesion (table 1). In all the 92 cases last

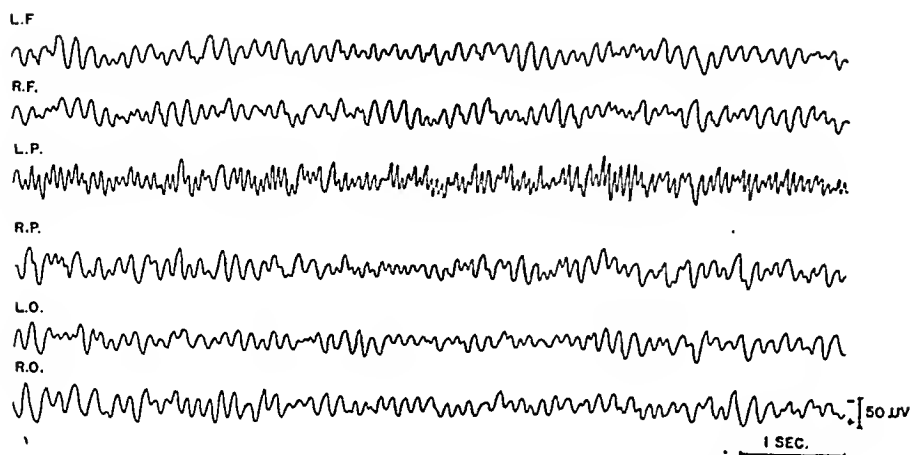


Fig. 3.—Focus of fast activity in the left parietal area of a girl aged 12 years. An injury to the head at the age of 2 years was followed in six months by right-sided convulsions, which continued with a frequency of six to ten per month, and by occasional petit mal seizures. The right arm and leg were weak.

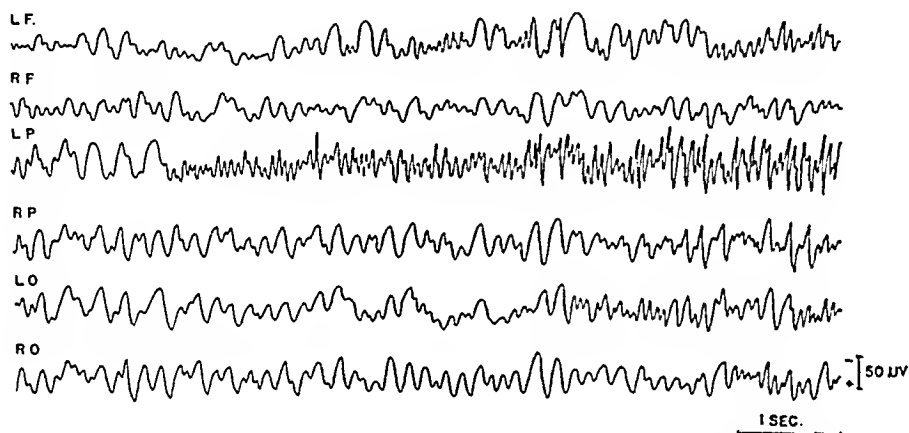


Fig. 4.—Focus of grand mal discharges in the left parietal area of a girl aged 19 years, who had a severe head injury four months before this paper was written. In the last twenty-four hours right-sided convulsions had appeared. At the time the electroencephalogram was taken the patient was in status epilepticus.

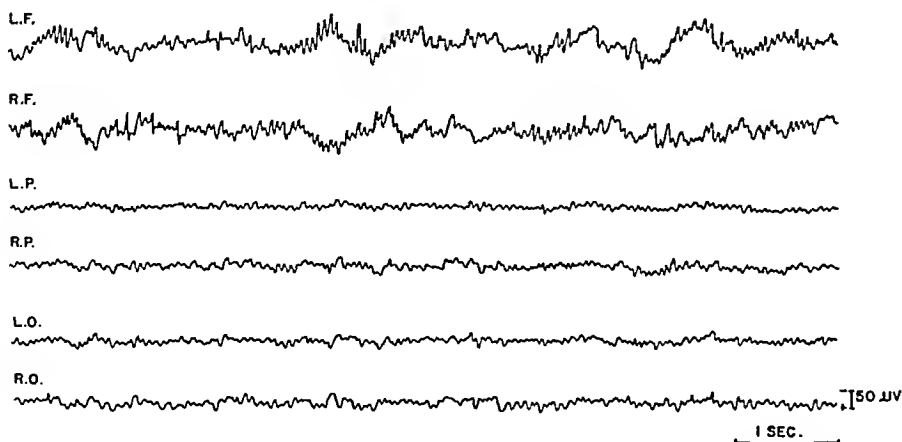


Fig. 5.—Focus of combined fast and $\frac{1}{2}$ to 2 per second activity in the frontal area of a man aged 25. One year before this paper was written a falling weight had lacerated the frontal lobes and severed the optic nerves. Generalized convulsions started six months later. Bilateral optic nerve atrophy and right hemiparesis were present.

mentioned the site of the electroencephalographic focus was in agreement with the clinical localization.

Examples of the various types of focal activity encountered in the electroencephalogram are shown in figures 1 to 10. The abnormal activity which appears so definitely localized in these cases is the same as that which appears as non-localized in other cases. In other words, any type of seizure discharge or electroencephalographic abnormality may be either focal or generalized. It is important, however, to recognize that certain types of disorder are more commonly localized

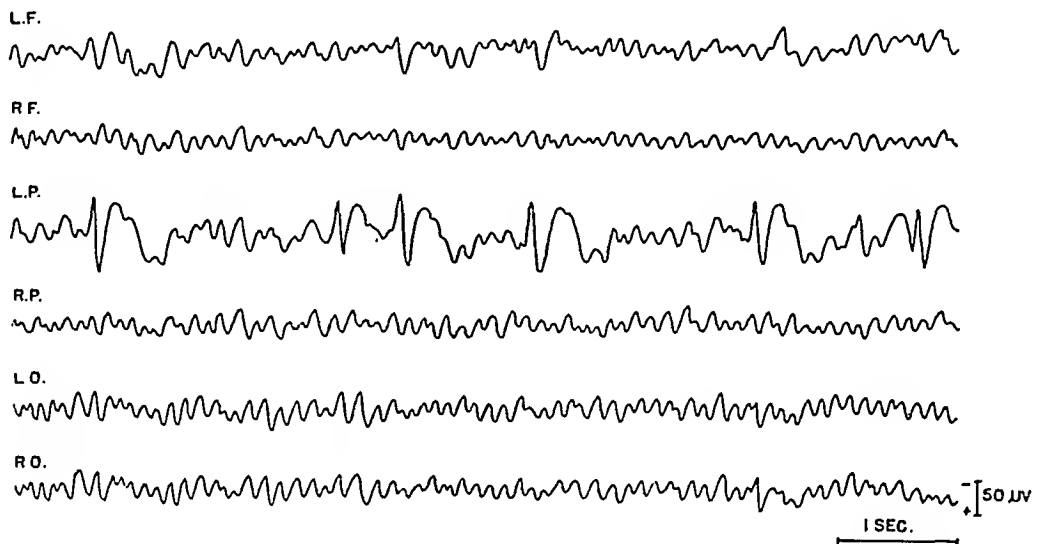


Fig. 6.—Focus of a petit mal variant type of activity in the left parietal area in a boy aged 12 years. A minor head injury, sustained two years before this paper was written, was followed two months later by generalized convulsions, which continued with a frequency of two to six per year. No focal neurologic signs were noted.

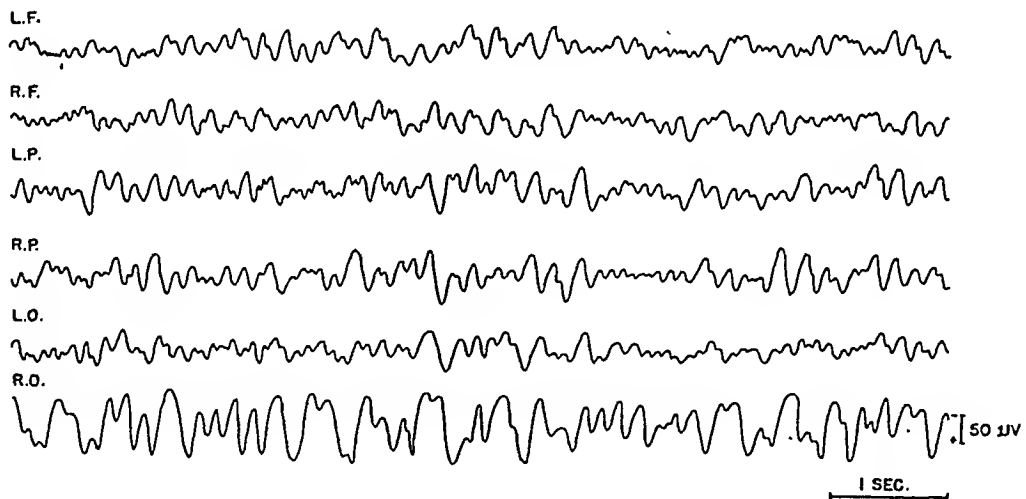


Fig. 7.—Focus of 3 to 6 per second waves in the right occipital area of a boy aged 11 years. Two years before this paper was written he had sustained a minor injury to the head, without loss of consciousness. The first convulsion occurred six weeks later. Convulsions had become progressively more severe and frequent. They were preceded by a visual aura of dancing stars on a black background. Weakness of the left leg was noted.

than others. This fact is clearly illustrated in figure 11, in which the percentage incidence of localized electroencephalographic activity of various types is contrasted with the percentage incidence of generalized disorders. Many foci show mixed types of disorder. Such foci have been classified according to whichever type of disorder predominated.

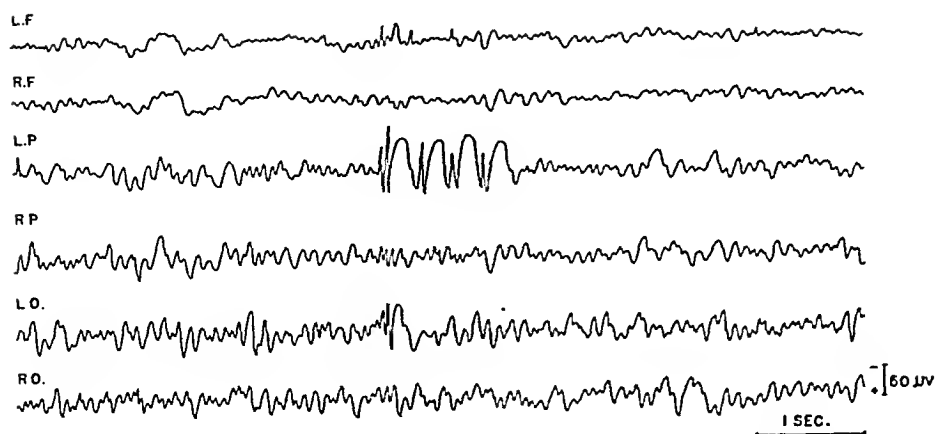


Fig. 8.—Focus of petit mal type of activity in the left parietal area of a boy aged 13 years. A fracture of the left frontotemporal region of the skull, sustained two months before this paper was written, was followed two days later by generalized convulsions. These seizures continued at a frequency of two to three per week, with numerous petit mal attacks.

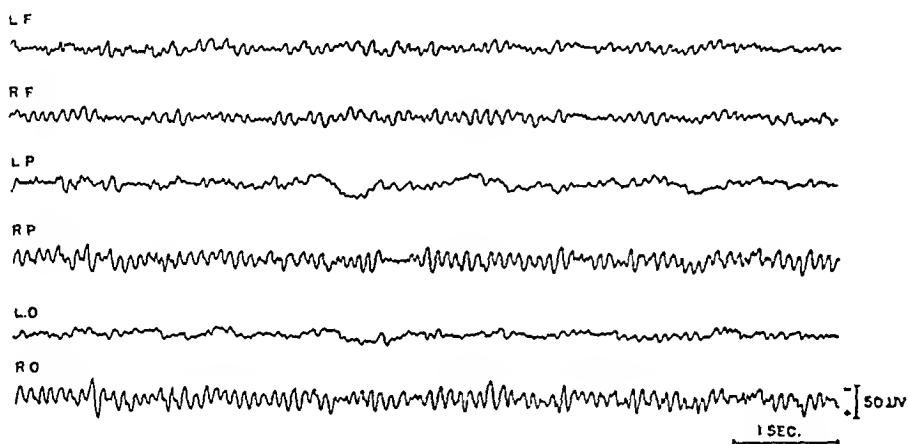


Fig. 9.—Focus of low amplitude activity in the left parietal and the left occipital area of a woman aged 41. Fracture of the left parieto-occipital area of the skull, seven years before this paper was written, was followed by right-sided and generalized convulsions a few months later, occurring with a frequency of several seizures per month. The right side was mildly paretic.

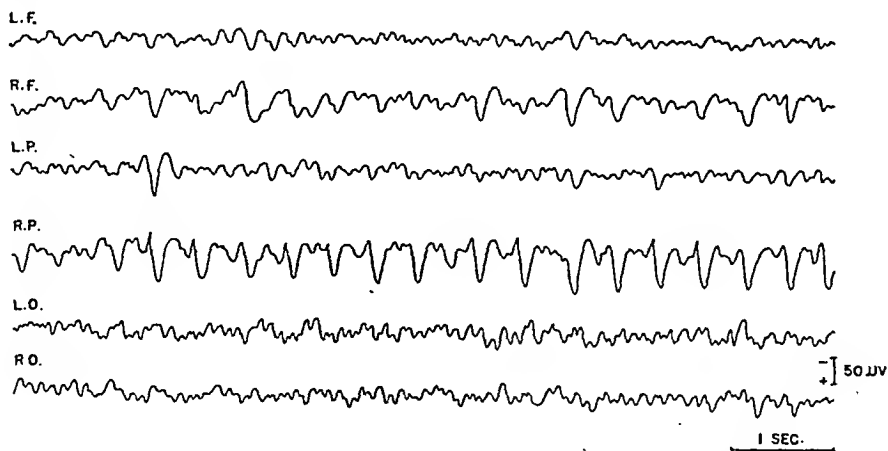


Fig. 10.—Focus of psychomotor type of activity in the right parietal area of a man aged 20, with a history of asphyxia neonatorum. Weakness of the left arm was first noticed at the age of 1 year. He was late in walking. Left-sided seizures developed at the age of 12 years, with an average frequency of one per month. Left hemiparesis was present.

In an analysis of the various types of electroencephalographic focal discharges, it was found that certain types were more often associated with clinical localizing signs than others, as shown in table 1. The highest association was noted when the electroencephalographic focal discharge was characterized by slow, irregular waves at the rate of 1 to 2 per second. A type of focal activity that was particularly stressed by Jasper,^{8b} consisting of spike discharges, was found to be a little less commonly associated with localized clinical signs. The lowest association occurred in cases in which the focal discharge was of the petit mal, or 3 per second wave and spike, type. In table 2 it may be seen that no one type of electroencephalographic focus is specific for a particular pathologic process; the incidence of different etiologic factors does, however, tend to vary somewhat according to the type of the focus.

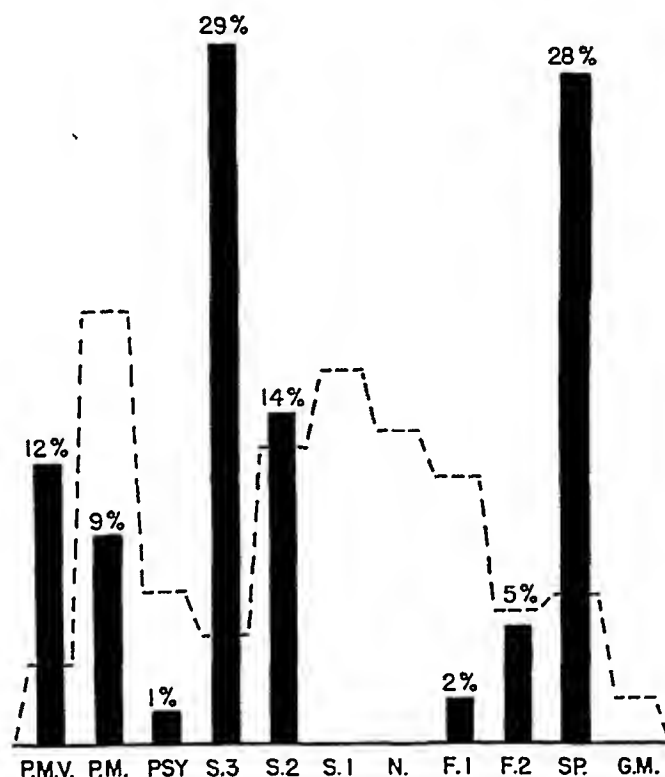


Fig. 11.—Distribution of electroencephalographic types of disorder in 160 cases of epilepsy with an electroencephalographic focus. The broken line indicates their distribution in the total series of 1,161 cases of epilepsy. *P.M.V.* indicates petit mal variant (2 per second wave and spike discharge); *P.M.*, petit mal (3 per second wave and spike discharge); *Psy.*, psychomotor (discharge of flat-topped, slow waves with a frequency of 2 to 4 per second, mixed with high voltage, 6 per second waves); *S.3*, very slow (fairly continuous $\frac{1}{2}$ to 3 per second) activity; *S.2*, slow (fairly continuous 3 to 6 per second) activity; *S.1*, slightly slow activity (moderate amount below 8 per second); *F.1*, slightly fast activity (moderate amount above 12 per second); *F.2*, fast activity (great amount above 12 per second); *Sp.*, spikes and single spike, and *G.M.*, grand mal seizure discharge. The *S* and *F* categories are adjusted for age. Examples of various types of activity are shown in figures 1 to 10. For a more detailed description of this classification, see Gibbs, Gibbs and Lennox.¹⁰

COMMENT

Since clinical evidence of localized damage to the brain was present in only 1 per cent of the cases without an electroencephalographic focus and in 58 per cent of those with an electroencephalographic focus (table 1), it appears that such damage is particularly common in cases of epilepsy in which electroencephalographic foci are present. As Jasper^{8b} has pointed out, the occurrence of seizures with an

electroencephalographic focus strongly suggests that the subject belongs to the group of epileptic patients who have seizures on an "organic basis," whereas seizures occurring without an electroencephalographic focus suggest that the subject belongs to the major group of epileptic patients who have seizures without a demonstrable "organic basis." The former group is generally referred to as having "symptomatic" and the latter as having "idiopathic" epilepsy.

Although there are undoubtedly important differences between seizures with and seizures without recognizable lesions in the brain, the appearance of the same general types of abnormal electrical activity with each suggests that they have a similar neurophysiologic basis. However, the fact that certain types of abnormal activity are more frequently encountered in cases with known pathologic conditions of the brain than in cases without such lesions suggests that certain disorders of nerve cell physiology are more or less peculiar to certain types of nerve cell injury.

TABLE 2.—*Percentage Incidence of Various Etiologic Agents Among Cases with Different Types of Electroencephalographic Focal Activity*

Type of Focal Activity		Trauma	Infection	Vascular Disease	Birth Injury	Developmental Defect	Cause Unknown	Total
$\frac{1}{2}$ to 2 per sec. (slow 3)...	Number.....	23	5	6	3	0	9	46
	Percentage.....	50	11	13	6	0	20	100
3 to 6 per sec. (slow 2)...	Number.....	11	2	2	1	0	6	22
	Percentage.....	50	9	9	5	0	27	100
Spikes.....	Number.....	15	5	3	2	2	18	45
	Percentage.....	33	11	7	5	4	40	100
Psychomotor.....	Number.....	0	0	0	1	0	1	2
	Percentage.....	0	0	0	50	0	50	100
18 to 22 per sec. (fast 2)	Number.....	6	3	0	0	1	1	11
	Percentage.....	55	27	0	0	9	9	100
Petit mal variant.....	Number.....	3	5	2	3	0	6	19
	Percentage.....	16	26	10	16	0	32	100
Petit mal.....	Number.....	5	0	0	2	1	6	14
	Percentage.....	36	0	0	14	7	43	100
Low amplitude.....	Number.....	0	0	1	0	0	0	1
	Percentage.....	0	0	100	0	0	0	100
Total.....	Number.....	63	20	14	12	4	47	160
	Percentage.....	39	13	9	7	3	29	100

Localizing signs in the electroencephalogram correlate highly with the clinical localization, but since many areas of the cortex are clinically silent, i. e., give no localizing signs in spite of the presence of a lesion, it is to be expected that many electroencephalographic foci will be unassociated with clinical evidence of localized disorder. The size of a focus and its location might be expected to determine its chance of being associated with clinical localizing signs. It is true that in all cases in which the electroencephalographic focus involved an entire hemisphere clinical localizing signs were present; as might be expected, also, a focus near the central sulcus was more often associated with localizing clinical signs than one in the frontal lobe. The type of electroencephalographic examination employed in the present study is capable of localizing disorders only in the accessible cortex, i. e., the outer convexity of the cerebral hemispheres; deep lesions cannot be localized. Therefore, in cases in which the clinical signs and symptoms point to a deep lesion, and such cases were rare in this series, there will be a poor correlation with the electroencephalographic focus. While it is probably true that in some of the 14 cases of epilepsy with clinical localization but without a electroencephalographic focus the lesion may have involved only deep structures, in no case was

this assumption definitely corroborated by the clinical evidence. In this series, failure to find a focus and discrepancies between the clinical and the electroencephalographic localization were not usually explicable on the basis of the inaccessibility of the lesion. For example, in 4 of the 31 cases in which typical jacksonian seizures of supposedly cortical origin occurred, repeated electroencephalographic examinations failed to reveal foci. Such failures are, for the most part, totally inexplicable and altogether disconcerting, but it is reassuring that the electroencephalographic focus was corroborative in 87 per cent of all cases with clinical localizing signs. This high degree of concordance is significant not only because it indicates the usefulness of electroencephalographic localization in cases of epilepsy, but because it tells something of the origin of seizures; it indicates that they occur rarely from localizable lesions in the depths of the brain.

A focus of electroencephalographic activity characterized by diminution in amplitude, as compared with the activity from the homologous area over the opposite hemisphere, was present in 1 case of cerebral hemorrhage. A focus of this type was described by Jasper, Kershman and Elvidge¹¹ in cases of subdural hematoma.

Except for minor differences in technic and nomenclature, the present study is in general accord with previous investigations by Jasper and his collaborators. It provides a statistical basis for some statements that were heretofore only feebly supported, and since it presents data on a large number of uniformly classified cases, it is serviceable for estimation of those expectancies which underlie all valid diagnoses and prognoses.

SUMMARY AND CONCLUSION

Electroencephalographic studies were carried out on a random sample of 1,161 epileptic patients. Simultaneous records from six cortical areas were made with monopolar leads. In 15 per cent, or 160 cases, electroencephalographic foci were found. In 58 per cent of these 160 cases clinical localizing signs were present, and in all these cases the clinical and electroencephalographic localizations were in agreement. A corroborating electroencephalographic focus was noted in 87 per cent of 106 cases with clinical localizing signs or symptoms.

Clinical evidence of localized damage to the brain was fifty-eight times as common in epileptic patients with electroencephalographic foci as in patients in whom the disturbance was generalized or absent. The same types of seizure discharge or other electroencephalographic abnormality were encountered in cases with focal electroencephalographic activity as in cases with nonfocal disorders. However, certain types of abnormality, notably irregular $\frac{1}{2}$ to 3 per second activity, spikes and 2 per second waves and spikes, were much commoner in focal than in nonfocal records. The presence of one of these three types of abnormality is presumptive evidence of localized damage to the brain.

Boston City Hospital.

11. Jasper, H. H.; Kershman, J., and Elvidge, A.: Electroencephalographic Studies of Injury to the Head, *Arch. Neurol. & Psychiat.* **44**:328-348 (Aug.) 1940.

EFFECT OF ELECTRICAL STIMULATION ON ATROPHY OF DENERVATED SKELETAL MUSCLE

D. Y. SOLANDT, M.D.

D. B. DeLURY, Ph.D.

AND

JOHN HUNTER, M.A.

TORONTO, CANADA

Reid¹ noted that a beneficial effect was produced by weak galvanic stimulation of denervated frog muscle. He pointed out that "the application to the treatment of certain cases of paralysis was so obvious as to require no comment." Langley² and Hartman, Blatz and Kilborn,³ from work with rabbits, concluded that electrical stimulation did not appear to benefit denervated muscle. Chor and associates,⁴ in work with monkeys, likewise found that electrical stimulation, as well as passive movement and massage, was ineffective, up to a period of at least six weeks after denervation, in retarding atrophy and degeneration of the denervated muscle. Fischer,⁵ using rats, demonstrated that electrical stimulation exerted a notable retarding influence on the loss in weight of denervated muscle. Such stimulation, Fischer observed, was accompanied by a distinctly higher degree of power in the denervated muscle and a slight decrease in the loss of birefringence, these effects, however, being of a lower order than the effect on loss of weight. Eccles⁶ and Hines⁷ found electrical stimulation effective in preventing loss of weight and made certain interesting observations on the optimum duration of stimulation. Gutmann and Guttman,⁸ from experiments with denervated rabbit muscles, concluded that galvanic stimulation delays and diminishes muscular atrophy. The return of the muscle to its initial volume after reinnervation was accelerated by such stimulation. These investigators also pointed out that treated muscles showed less fibrosis, larger fibers, more definite striation, better excitability and contractility on direct stimulation and stronger reflex action than untreated muscles.

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc. From the Departments of Mathematics, Physiological Hygiene and Physiology, University of Toronto.

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5. Fischer, E.: The Effect of Faradic and Galvanic Stimulation upon the Course of Atrophy in Denervated Skeletal Muscles, Am. J. Physiol. **127**:605, 1939.

6. Eccles, J. C.: Disuse Atrophy of Skeletal Muscle, M. J. Australia **2**:160, 1941.

7. Hines, H. M.: Effects of Immobilization and Activity on Neuromuscular Regeneration, J. A. M. A. **120**:515 (Oct. 17) 1942.

8. Gutmann, E., and Guttman, L.: Effect of Electrotherapy on Denervated Muscles in Rabbits, Lancet **1**:169, 1942.

The experimental evidence summarized in the foregoing review weighs heavily toward the view that electrical treatment is effective in retarding the course of atrophy in denervated muscle.

The present investigation was undertaken to determine the effect of variations in electrical stimulation on the reduction in atrophy of denervated muscle. An attempt was made (1) to compare the relative effectiveness of 25 cycle sinusoidal, 60 cycle sinusoidal, faradic and galvanic currents and (2) to determine the optimum number and length of treatments.

METHOD

Albino rats weighing 150 to 200 Gm. were used. The same strain of rats has been used in experiments dealing with the denervation of skeletal muscles on a number of previous occasions,⁹ and the changes occurring in such muscles have been evaluated and found to occur with remarkable constancy. The animals received a full normal diet and were kept in individual cages. The gastrocnemius-soleus group of muscles was denervated on one side of each animal by excision of a small section of the sciatic nerve high in the thigh. Initially

TABLE 1.—*Factorial Experimental Design*

Factors		Levels	Symbols
Number of treatment periods daily (1; 3; 6)		3	a ₁ , a ₂ , a ₃
Length of treatment (1 min.; 2 min.; 3 min.; 5 min.)		4	b ₁ , b ₂ , b ₃ , b ₄
Current type (galvanic; faradic; 60 cycle; 25 cycle)		4	c ₁ , c ₂ , c ₃ , c ₄

Length of Treatment, Min.	Type of Current	Number of Treatment Periods Daily		
		One	Three	Six
1	Galvanic.....	a ₁ b ₁ c ₁	a ₂ b ₁ c ₁	a ₃ b ₁ c ₁
	Faradic.....	a ₁ b ₁ c ₂	a ₂ b ₁ c ₂	a ₃ b ₁ c ₂
	60 cycle.....	a ₁ b ₁ c ₃	a ₂ b ₁ c ₃	a ₃ b ₁ c ₃
	25 cycle.....	a ₁ b ₁ c ₄	a ₂ b ₁ c ₄	a ₃ b ₁ c ₄
2	Galvanic.....	a ₁ b ₂ c ₁	a ₂ b ₂ c ₁	a ₃ b ₂ c ₁
	Faradic.....	a ₁ b ₂ c ₂	a ₂ b ₂ c ₂	a ₃ b ₂ c ₂
	60 cycle.....	a ₁ b ₂ c ₃	a ₂ b ₂ c ₃	a ₃ b ₂ c ₃
	25 cycle.....	a ₁ b ₂ c ₄	a ₂ b ₂ c ₄	a ₃ b ₂ c ₄
3	Galvanic.....	a ₁ b ₃ c ₁	a ₂ b ₃ c ₁	a ₃ b ₃ c ₁
	Faradic.....	a ₁ b ₃ c ₂	a ₂ b ₃ c ₂	a ₃ b ₃ c ₂
	60 cycle.....	a ₁ b ₃ c ₃	a ₂ b ₃ c ₃	a ₃ b ₃ c ₃
	25 cycle.....	a ₁ b ₃ c ₄	a ₂ b ₃ c ₄	a ₃ b ₃ c ₄
5	Galvanic.....	a ₁ b ₄ c ₁	a ₂ b ₄ c ₁	a ₃ b ₄ c ₁
	Faradic.....	a ₁ b ₄ c ₂	a ₂ b ₄ c ₂	a ₃ b ₄ c ₂
	60 cycle.....	a ₁ b ₄ c ₃	a ₂ b ₄ c ₃	a ₃ b ₄ c ₃
	25 cycle.....	a ₁ b ₄ c ₄	a ₂ b ₄ c ₄	a ₃ b ₄ c ₄

alternate sides were denervated, but ultimately the selection of the limb to be denervated was made at random. The latter procedure resulted in approximately equal numbers of rats with denervation of the right leg and rats with denervation of the left leg and conformed to the statistical treatment accorded the results.

In preliminary work the effects of a 25 cycle sinusoidal current were studied to determine the optimum number of stimulation periods each day and the optimum length of each stimulation period. Stimulation was accomplished with a current strength of 2.5 milliamperes. The intensity of the 60 cycle sinusoidal, faradic and galvanic currents was adjusted to equal that employed with the 25 cycle sinusoidal current and was maintained at this value for the duration of the experiment. The intensity was supramaximal for all but the late faradic stimulation. Observations on a small independent series of animals given supramaximal 25 cycle and supramaximal faradic stimulation simply confirmed the results for the main series.

Electrical stimulation of the limb was accomplished by placing the animal in a plaster of paris cast fitted over the dorsal portion of the head and body. A sheet of transparent xylonite

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placed ventrally held the animal in the cast while it was being placed and clamped in position. To facilitate the handling of the animal during this procedure, light ether anesthesia was used. Electrical connections were made to the appropriate protruding leg through a clip on the skin of the thigh and another on the toes. Each animal received a five second period of stimulation, followed by a five second period of rest for a total period of one, two, three or five minutes. The durations of the periods of stimulation and rest were accurately controlled by a motor-driven commutator. Each experiment was conducted for a period of fourteen days, and stimulation in each case was started on the third day after denervation.

For the purpose of applying a standard statistical treatment to the weights of the denervated muscles obtained on the fourteenth day, a factorial experimental design was used, which is summarized in table 1. This design requires that each level of each factor, such as the number of treatment periods daily, the length of treatment and the type of current, be taken in combination with each level of every other factor. In this experiment the factors considered were as follows:

Factors	No. of Levels	Symbols
Number of treatment periods (1, 3, 6).....	3	a_1, a_2, a_3
Length of treatment (1 min.; 2 min.; 3 min.; 5 min.)....	4	b_1, b_2, b_3, b_4
Type of current (galvanic; faradic; 60 cycle; 25 cycle) ..	4	c_1, c_2, c_3, c_4

Thus, there were $4 \times 4 \times 3$, or 48 distinct combinations. One rat was assigned to each combination, and although the treatment received by each rat differed from that received by every other rat, nevertheless comparisons of treatments could validly be made. For example, 12 rats were assigned to each type of current. Differences in the responses of these sets of 12 rats would presumably indicate differences resulting from the various types of current applied, because all other treatments were equally represented in each of these sets of 12 rats. A replication of the original number of observations assigned to the identical kind, length and number of treatments provided a total of 96 observations. The weight of the normal muscle was included as a covariant.

RESULTS

The weights of the normal and the denervated gastrocnemius-soleus muscle groups obtained for each combination of factors are set forth in table 2. When these values were submitted to a standard statistical analysis of variance and covariance,¹⁰ the values recorded in table 3 were obtained. Table 3 shows the sums of squares of deviations from the mean of the weights of the denervated muscles adjusted by covariance to a normal weight of 1.18 Gm. In this table, the "error" mean square, 48.08, shows the magnitude of the variation which results from the errors of the experiment, usually ascribed to chance. The symbol A stands for a comparison among themselves of the averages obtained for one application (a_1), three applications (a_2) and six applications (a_3) daily. The mean square corresponding to A acquires its value from the differences in response to a_1 , a_2 and a_3 . If these responses had been identical, this mean square would have the value zero. If the responses differed only through the errors of the experiment, the mean square should not differ greatly from that ascribable to such errors alone, that is, 48.08. Actually, the mean square corresponding to A is 220.60, which is vastly greater than 48.08, as judged by an objective test, the analysis of variance test, and therefore must have resulted from real differences in response to a_1 , a_2 and a_3 .

Exactly similar considerations apply to C. In the case of B, however, the mean square is not substantially greater than the "error" mean square. Hence there was no evidence in this experiment that variation in the length of treatment produced variation in response.

10. Fisher, R. A.: *Statistical Methods for Research Workers*, Edinburgh, Oliver & Boyd, 1934. Rider, P. R.: *An Introduction to Modern Statistical Methods*, New York, John Wiley & Sons, 1939.

The symbol of $A \times C$ represents the interaction of A and C, that is, the variation in the responses to a_1 , a_2 and a_3 , according as c_1 , c_2 , c_3 or c_4 is employed and vice versa.

Under "error" are included all interactions which involve the replication.

TABLE 2.—Weights of Normal and of Denervated Muscle* Following Treatment Assigned in the Factorial Experimental Design

Length of Treatment, Min.	Type of Current	Number of Treatment Periods Daily					
		One		Three		Six	
		Denervated Muscle	Normal Muscle	Denervated Muscle	Normal Muscle	Denervated Muscle	Normal Muscle
Fourteenth Day After Denervation							
1	Galvanic	72	152	74	131	69	131
	Faradic	61	130	61	129	65	126
	60 cycle	62	141	65	112	70	111
	25 cycle	85	147	76	125	61	130
2	Galvanic	67	136	52	110	62	122
	Faradic	60	111	55	180	59	122
	60 cycle	64	126	65	190	64	93
	25 cycle	67	123	72	117	60	92
3	Galvanic	57	120	66	132	72	129
	Faradic	72	165	43	95	43	97
	60 cycle	63	112	66	130	72	180
	25 cycle	56	125	75	130	92	162
5	Galvanic	57	121	56	160	78	135
	Faradic	60	87	63	115	53	118
	60 cycle	61	93	79	126	63	160
	25 cycle	73	108	86	140	71	120
Weights of Normal and Denervated Muscle Obtained in a Replication of the Above Experiment							
1	Galvanic	46	97	74	131	53	81
	Faradic	60	126	64	124	52	102
	60 cycle	71	129	64	117	71	103
	25 cycle	53	103	65	103	66	103
2	Galvanic	44	83	53	117	51	97
	Faradic	57	104	55	112	51	100
	60 cycle	62	114	61	100	79	115
	25 cycle	60	105	73	112	82	102
3	Galvanic	53	101	50	103	61	115
	Faradic	56	120	57	110	56	105
	60 cycle	56	101	56	109	71	105
	25 cycle	56	97	53	87	69	107
5	Galvanic	46	107	55	103	64	115
	Faradic	56	109	55	104	57	103
	60 cycle	64	114	66	101	62	99
	25 cycle	59	102	53	98	83	135

* Weights are expressed in grams, multiplied by the factor 100.

TABLE 3.—Statistical Summary

Source	Adjusted Sums of Squares of Deviations from Mean of Weights of Denervated Muscle	Degrees of Freedom	Mean Square
Replications.....	0.23	1	
A.....	441.21	2	220.60*
B.....	180.53	3	60.17
C.....	2,111.04	3	703.68*
A × B.....	211.78	6	35.29
A × C.....	861.60	6	143.60†
B × C.....	404.36	9	44.93
A × B × C.....	627.83	18	34.83
Error.....	2,211.93	46	48.03
Total.....	7,050.66	94	

* Significant at the 1 per cent level.

† Significant at the 5 per cent level.

COMMENT AND CONCLUSIONS

Table 4 exhibits most of the conclusions to be drawn from the factorial experiment. Similar tables made up for a and b and for b and c add nothing, owing

to the absence of effect of variations in the length of treatment. The 25 cycle current (c_4) produced consistently the best results, and the 60 cycle current (c_3), consistently the second best results. Both types were distinctly superior to either the galvanic or the faradic current. No demonstrable difference was detected in the effect of the faradic and that of the galvanic current on retention of weight. Neither current performed consistently better than the other. This lack of consistency accounts for most of the inflation of the $A \times C$ interaction (table 3).

The variation in the number of treatments given daily (a_1, a_2, a_3) produced significant variations in response, and the effectiveness of the treatments increased with the number of treatments given daily. The retention of weight varied in an approximately linear manner with the number of treatments given daily, as is shown by the fact that the linear component accounts for 434.36 out of the total sum of squares of 441.21. (This linear component is calculated with regard to the numbers a_1, a_2 and a_3 as being in arithmetical progression. Actually, $a_1 = 1, a_2 = 3$ and $a_3 = 6$, and if this departure from arithmetical progression were taken into account, still more of the total sum of squares would be absorbed by the linear component.) A small supplementary experiment seemed to show that this linearity extends beyond the range of number of treatments used in this series (one to six treatments daily).

TABLE 4.—*Weight of Denervated Muscle Adjusted to a Normal Weight of 1.18 Gm.**

	a_1	a_2	a_3	Totals
c_1	56	59	65	60
c_2	60	56	57	58
c_3	63	64	69	65
c_4	65	72	73	70
Totals.....	61	63	66	63

* Coefficient of regression of weight of denervated muscle on normal weight = 0.2483.

Although the experiment would detect as significant differences in response of the order of 5 per cent of the normal weight, no sensible differences in result were obtained by varying the length of treatment. It appears, then, that the length of time assigned to the treatment is of no consequence, at least within the range investigated (one to five minutes). Eccles,⁶ likewise, found the length of each treatment to have little effect on the atrophy.

In view of the fact that electrical stimulation does reduce the loss of weight of denervated muscles, the direct linear relationship between retention of weight and repetition of the periods of treatment appears reasonable. The lack of relationship between duration of individual treatments and effectiveness is not so obvious. It is improbable that the shortest period used could cause appreciable fatigue and thus, in effect, be too long. Possibly the beneficial result was entirely due to improvement in the circulation to the muscle. Perhaps a specific increase in the venous return from the muscle was brought about. If improved venous return was the mechanism, a short period of maximal contraction would be as effective in reducing loss of weight as a prolonged contraction.

Only two frequencies of sinusoidal current were tested. In these experiments a 25 cycle current gave better results than a 60 cycle current. The reason for the greater effectiveness of the lower frequency is not known. Possibly fatigue to the lower frequency differs from that to the higher. More probably the time

factors of excitation (Lapicque's chronaxia) and accommodation (Hill's lambda) of the muscle are such that there is a definite optimum frequency of stimulation,¹¹ which in the present case was probably in the neighborhood of 25 cycles.

SUMMARY

That electrical stimulation is effective in reducing the loss of weight of denervated muscle has been demonstrated conclusively by a number of workers. With electrical stimulation at maximal strength, the present experiments led to the following conclusions:

1. Of the types of current tried, the 25 cycle alternating (sinusoidal) current produces the best results with respect to retention of weight, and the 60 cycle current is second best.
2. Neither galvanic nor faradic current performs consistently better than the other. Both are inferior to the 25 and the 60 cycle sinusoidal current.
3. The effectiveness of the treatments increases with the number of treatments daily. This relationship is apparently linear.
4. No sensible differences in results are obtained by varying the length of the treatment within the limits employed (one to five minutes).

University of Toronto.

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INTERACTION OF ELECTRIC SHOCK AND INSULIN HYPOGLYCEMIA

EXPERIMENTAL INVESTIGATIONS

E. GELLHORN, M.D., Ph.D.

AND

M. KESSLER, M.S.

CHICAGO

The present study is a further attempt to contribute to an understanding of the essential physiologic mechanisms set up by electric shock and insulin hypoglycemia. Our earlier investigation¹ showed that electrically induced convulsions excite in the unanesthetized rat the sympatheticoadrenal and vagoinsulin systems. However, the action on the vagoinsulin system is masked in the normal animal by the predominance of the excitation of the sympatheticoadrenal system, which causes hyperglycemia.

Studies by one of us (E. G.), in collaboration with Ingraham, Moldavsky, Kiely, Kraines and Hamilton,² have suggested that hypoglycemia likewise produces increased excitability of the sympathetic medullary centers, since the reaction of the blood pressure to anoxia, as well as to carbon dioxide, is greatly increased during hypoglycemia. Moreover, the increased secretion of epinephrine during hypoglycemia is well known.³ That the effect is not restricted to the sympathetic division of the autonomic nervous system is evident from the fact that gastric secretion and motility are increased and the heart rate is diminished in insulin shock.⁴

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From the Department of Physiology, the University of Illinois College of Medicine.

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If it is true that electric shock and hypoglycemia produce predominantly an excitation of the sympathetic centers, it must be assumed that conditions which permit the interaction of these factors will bring the sympathetic effects into great prominence. The experiments described in this paper were designed to test this hypothesis. It was decided, therefore, to study the effect of electric shock at normal blood sugar levels and during insulin hypoglycemia.

The experiments were performed on adrenodemedullated rats for two reasons. First, insulin coma is induced with greater regularity and with smaller doses of insulin in the demedullated animal than in the normal one. Second, it was thought that the action of electric shock on the sympathetic centers under the aforementioned conditions could be better evaluated if the effect of sympathetic stimulation on the blood sugar was eliminated. Since a rise in blood sugar will promptly cause disappearance of all symptoms of hypoglycemia, the excitation of the sympathicoadrenal system by electric shock will terminate the coma through restoration of the normal blood sugar. Under these conditions the effect of the sympathetic stimulation, if any, would be obscured. As indicators of the effect of insulin hypoglycemia and of electric shock were chosen the electroencephalogram and the behavior of the rats, the blood sugar and, finally, the heart rate.

METHOD

From male rats, weighing 250 to 300 Gm., the medulla of both adrenal glands was removed, and the animals were used one or more weeks after the operation. The electroencephalogram was obtained by means of phonograph needles inserted in the skull (Hoagland), and the electric shock current was applied through the same electrodes. Power for the shock was obtained from a General Electric variable autotransformer set at 40 volts and delivering a current of 30 milliamperes for one to two seconds.⁵ Insulin⁶ was injected intraperitoneally (5 units per kilogram of body weight), and at the height of hypoglycemic coma (usually forty to sixty minutes after the injection of insulin) the electric shock was applied and its action on the electroencephalogram, the general behavior and the pulse rate was studied. The blood sugar was determined according to the method of Shaffer and Hartman or of Hoffman.⁷ The values obtained with the latter method are about 30 mg. per hundred cubic centimeters higher than those obtained with the former.

RESULTS

Effects of Electric Shock on the Electroencephalogram of Rats.—Numerous experiments performed on normal and on adrenodemedullated rats showed uniform changes in the clinical picture, as well as in the electroencephalogram, after electric shock. The first stage was characterized by tonic-clonic convulsions, followed by a catatonic state, in which the rat could be maintained in an abnormal posture for several minutes. Hereafter, a gradual return to normal locomotion and behavior took place. During the convulsions the electroencephalogram showed spikes of high amplitude characteristic of seizures. They were followed by a period of complete or almost complete silence. Then the potentials were gradually restored to normal during the next ten to sixty minutes. The alpha potentials were at

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first low and attained the normal amplitude after several minutes. In some instances they were normal in three minutes, but in a few cases their amplitude was still diminished sixty minutes after shock, when the behavior of the rat was normal. Most characteristic was the occurrence of delta potentials after the period of complete silence. As a rule they appeared before the alpha potentials and decreased in amplitude gradually, while the alpha potentials came more and more into prominence. In no instance was the amplitude of the alpha potentials increased above the normal level.

Figure 1 shows the electroencephalogram before (1) and shortly after (2) application of the electric shock. The large potentials in the first half of the record coincide with the end of the convulsive period. Record 3 illustrates the period

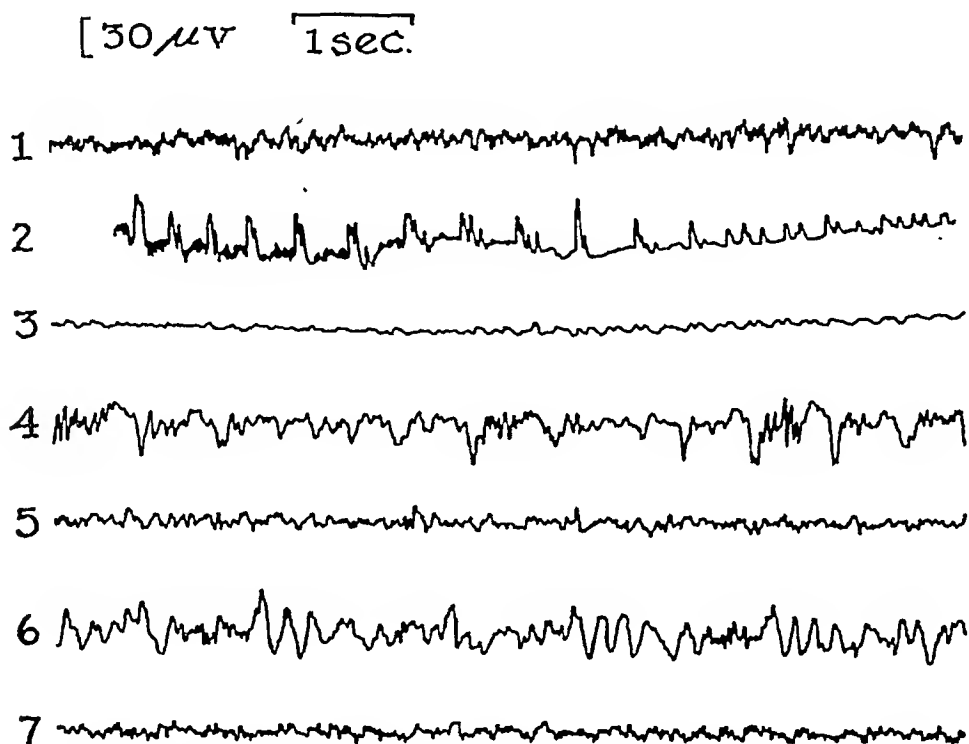


Fig. 1.—Effect of electric shock (40 volts; 30 milliamperes) on the electroencephalogram of the rat. Record 1 was made before shock; records 2 to 7 were obtained one-half, three, four and a half, seven and twenty minutes respectively after shock.

of almost complete silence which follows the period of convulsions. This stage is succeeded by the stage shown in record 4, in which the delta potentials become prominent. In the next period the alpha potentials have returned to a considerable extent, although their amplitude is low. A few minutes later a record (6) was obtained in which the delta potentials had again become more prominent. Such a recurrence of delta potentials was not infrequent. The final record (7) shows the reestablishment of normal potentials. At this time the rat appeared normal. Removal of the medulla of the adrenals did not alter the effect of electric shock on the electroencephalogram and the behavior of the animal.

Effect of Electric Shock on Hypoglycemic Rats.—In order to evaluate the effect of electric shock on hypoglycemic rats it was necessary to study the action of insulin hypoglycemia in control experiments. In general, it was found that the adrenomedullated rats when given an injection of 2 to 5 units of insulin per

kilogram of body weight showed hypoglycemic convulsions in forty to sixty minutes and died shortly after the onset of convulsions unless dextrose was administered. If in the state of maximal hypoglycemia a very small amount of dextrose was injected intraperitoneally, coma persisted and convulsions were prevented. Under these conditions the electroencephalogram showed the typical hypoglycemic picture. If the animal was kept in this condition for one hour or more, the subsequent injection of an adequate amount of sugar, although leading to distinct hyperglycemia, failed to bring about recovery.

In the experiment illustrated in figure 2, 12 mg. of dextrose injected during insulin coma permitted the animal to remain in coma for almost an hour and kept the blood sugar at a low level. No convulsions occurred during this time. The electroencephalogram showed a decline of both the alpha and the delta potentials

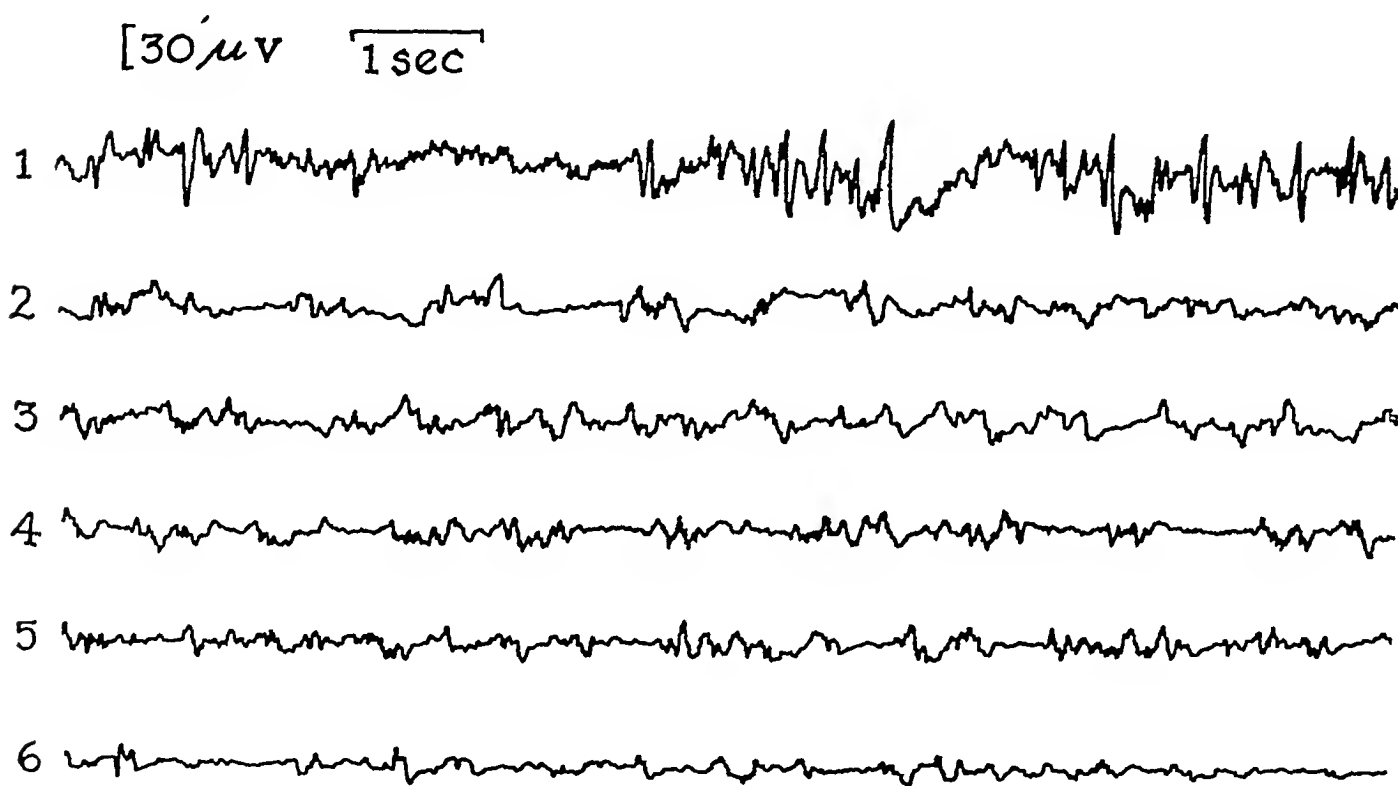


Fig. 2.—Effect of prolonged insulin coma on the adrenodemedullated rat.

10:05 a. m.: 5 units of insulin per kilogram of body weight.

Record 1.—10:53 a. m.: Coma.

11:07 a. m.: Blood sugar level 58 mg. per hundred cubic centimeters.

11:08 a. m.: Intraperitoneal injection of 5 mg. of dextrose.

Record 2.—11:10 a. m.: Coma.

Record 3.—11:14 a. m.: Coma.

Record 4.—11:23 a. m.: Coma, blood sugar 54 mg. per hundred cubic centimeters.

11:25 a. m.: Intraperitoneal injection of 7 mg. of dextrose.

Record 5.—11:28 a. m.: Coma.

Record 6.—11:46 a. m.: Coma.

11:48 a. m.: Blood sugar 58 mg. per hundred cubic centimeters; 14 mg. of dextrose injected intraperitoneally.

11:56 a. m.: Coma; 420 mg. of dextrose injected intraperitoneally; coma continued.

12:25 a. m.: Convulsions; animal died.

The experiment shows progressive deterioration of the electroencephalogram of an animal in prolonged coma maintained at a constant level of the blood sugar.

during this period. At the beginning of the coma (1) large delta potentials were interspersed among normal alpha waves. At the end of the coma (6) even the slow potentials were small, and there were relatively long periods with little or no electrical activity. These changes seemed to indicate gradual deterioration of cerebral function, since injection of an adequate amount of dextrose failed to relieve coma and the electroencephalographic abnormalities. Finally, the animal died in convulsions.

On the basis of these control experiments, investigations were carried out in which at the height of the hypoglycemic symptoms convulsions were produced by the application of an electric shock to the head. Successful experiments were performed on 13 adrenomedullated rats, in which the electric shock led to complete or almost complete recovery from the coma. It is noteworthy that in only 2 of these rats did the blood sugar rise above coma levels. In all the others the level of the blood sugar remained practically unchanged. This is understandable in view of the fact that hyperglycemia results from electric shock in the normal but not in the adrenomedullated rat. This statement is apparently valid for the adrenomedullated rat in the hypoglycemic state.

The interesting observation that electric shock may cause recovery from hypoglycemic coma without alteration in the low level of the blood sugar is based not only on the behavior of the animals but on electroencephalographic records. The record obtained from the first rat (fig. 3 *A*) shows that coma was observed when the blood sugar had fallen to 62 mg. per hundred cubic centimeters.⁸ Nineteen minutes after the onset of coma (3) the electroencephalogram showed large, slow delta waves interspersed with occasional alpha waves. Then convulsions were induced electrically. After they had disappeared, both grossly and in the electroencephalographic record, the characteristic period of almost complete silence appeared in the electroencephalogram (4). Records obtained nine and twenty-one minutes later showed that the delta potentials, which were very large prior to the electric shock, were now relatively infrequent and smaller in amplitude and that alpha potentials had reappeared and had gradually increased in amplitude (compare 6 and 5). With the reappearance of a nearly normal electroencephalogram the behavior of the rat had changed fundamentally. Whereas prior to the application of the electric shock the righting reflex was completely absent, it was seen later (ten minutes after the shock) that the rat made a slight attempt to right itself when placed on its back, and during the taking of record 6 it appeared perfectly normal in spite of the fact that the blood sugar reading at that time was completely unchanged.

The second set of records (*B*) in figure 3 shows the typical development of the electroencephalographic symptoms of insulin hypoglycemia, characterized by large delta potentials. After electric shock an electroencephalogram was obtained in which the delta potentials were far less prominent. Such slight delta potentials as appeared in record 6 are frequently seen in normal rats. Comparison of record 6 with record 1, obtained prior to the injection of insulin, shows that the normal electroencephalogram has been reestablished to a considerable degree, although in this experiment the clinical recovery was less than in the preceding observation. No spontaneous locomotion was observed, but the righting reflexes, which had disappeared prior to the electric shock, were at least partially restored. Here, again, the blood sugar remained unchanged at a coma level in spite of the partial restoration of cerebral function.

The third set of records (*C*) illustrates, again, the far reaching restoration of the electroencephalogram and the behavior of the rat to normal after electric shock, although the blood sugar was at a still lower level than was observed in the first two experiments shown in figure 3.

Figure 4 illustrates a type of recovery which was somewhat different from that shown in figure 3. During coma (1) the electric activity was slight, consisting of slow waves occurring at regular intervals. We have frequently observed

8. Determined by the method of Hoffman.

this type of electroencephalogram as the only sign of electric activity when the animal was in deep coma. After the electric shock there was a reappearance of distinct alpha waves, as well as periods of large potentials in the form of spindles,

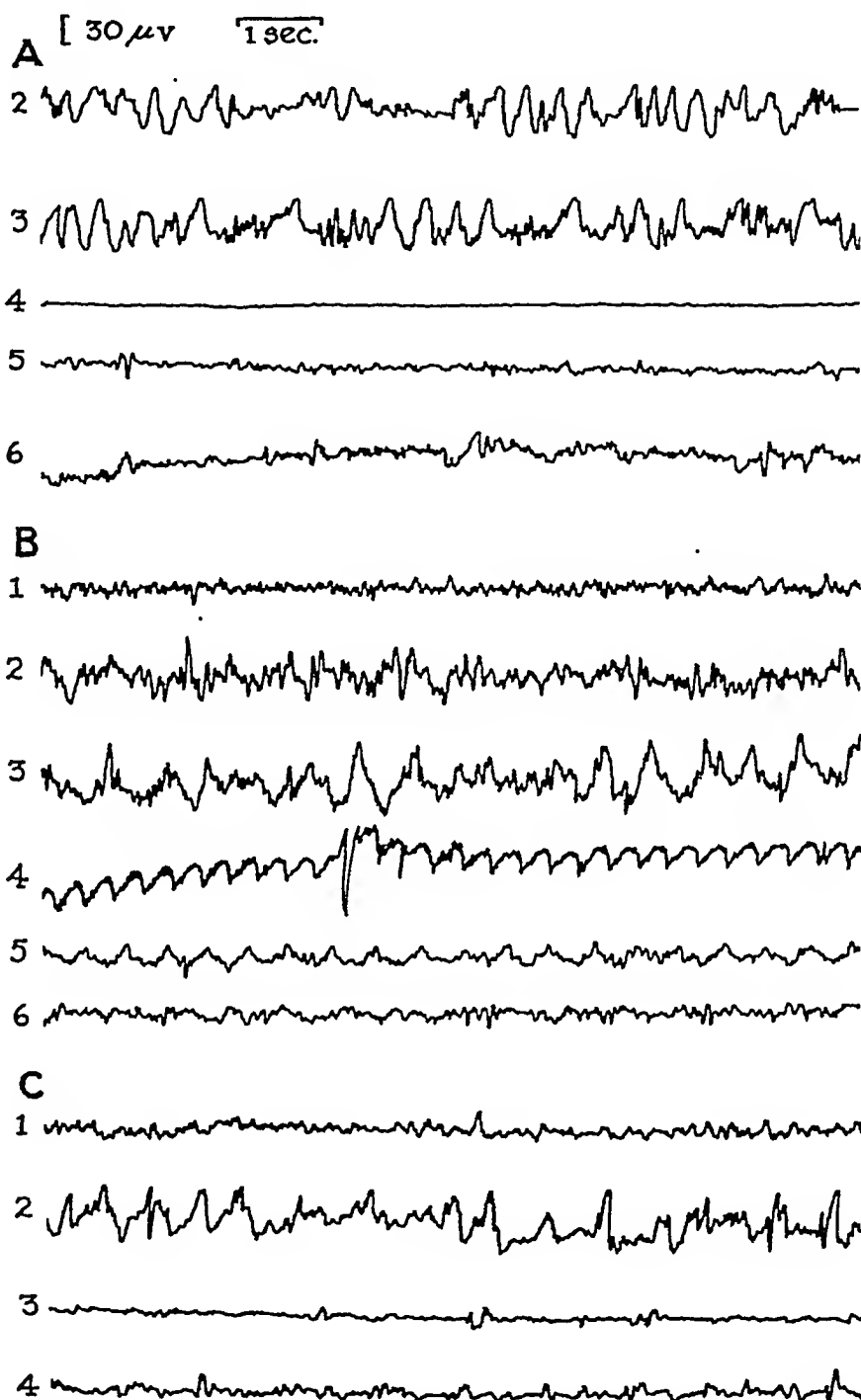


Fig. 3.—Effect of electric shock on the electroencephalogram and the behavior of adrenalectomized rats in hypoglycemic coma.

Set A.—2:50 p. m.: 5 units of insulin per kilogram of body weight.

Record 2.—3:50 p. m.: Coma.

3:53 p. m.: Blood sugar 62 mg. per hundred cubic centimeters.

Record 3.—4:09 p. m.: Coma.

4:10 p. m.: Electric shock.

Record 4.—4:14 p. m.: Coma.

Record 5.—4:23 p. m.: Partial righting reflex.

4:29 p. m.: Behavior almost normal.

4:31: Blood sugar 62 mg. per hundred cubic centimeters.

Record 6.—4:35 p. m.: Behavior normal.

Set B.—1:10 p. m.: 5 units of insulin per kilogram of body weight.

Record 1.—1:30 p. m.: Rat normal.

Record 2.—1:59 p. m.: Coma.

Record 3.—2:14 p. m.: Coma.

2:16 p. m.: Slight convulsion.

2:18 p. m.: Electric shock.

2:25 p. m.: Blood sugar 62 mg. per hundred cubic centimeters.

Record 4.—2:26 p. m.: Coma.

Record 5.—2:35 p. m.: Partial righting reflex.

Record 6.—2:45 p. m.: Partial righting reflex.

2:50 p. m.: Blood sugar 62 mg. per hundred cubic centimeters.

Set C.—9:28 a. m.: 5 units of insulin per kilogram of body weight.

Record 1.—10:10 a. m.

Record 2.—10:30 a. m.: Coma.

10:30½ a. m.: Electric shock.

Record 3.—10:39 a. m.: Blood sugar 54 mg. per hundred cubic centimeters.

Record 4.—11: a. m.: Rat normal; blood sugar 58 mg. per hundred cubic centimeters.

similar to those occurring during anoxia⁹ and sleep.¹⁰ In this experiment, also, there was clinical recovery associated with improvement in the electroencephalogram in spite of the persistence of a very low blood sugar level.

The experiments illustrated in figures 3 and 4 make it clear that electrically induced convulsions may bring about either partial or complete recovery in hypoglycemic animals in spite of unchanged low levels of the blood sugar. The degree of recovery varies somewhat with different animals, and there was no complete parallelism between the electroencephalographic and the clinical recovery. These observations indicate that mechanisms are activated during the electrically induced convulsions which greatly improve the function of the brain. Our studies suggest that spontaneous convulsions may have a similar effect.

It was stated earlier that when adrenodemedullated rats are given injections of an adequate amount of insulin, hypoglycemic coma occurs and is followed by convulsions, which usually result in death unless dextrose is injected immediately. We have, however, observed occasionally a somewhat different course, which is

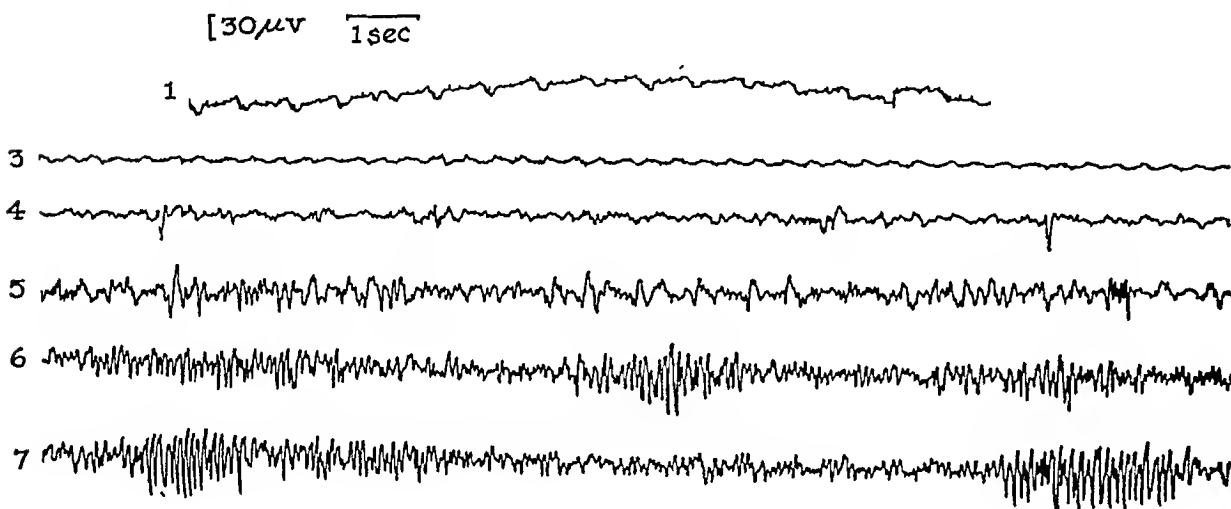


Fig. 4.—Effect of electric shock on the electroencephalogram of a adrenodemedullated rat in hypoglycemic coma. Five units of insulin per kilogram of body weight was injected.

Record 1.—Coma, one hour after injection of insulin; blood sugar 32 mg. per hundred cubic centimeters.

Record 3.—Two minutes after shock.
Record 4.—Five minutes after shock.

Record 5.—Ten minutes after shock.

Record 6.—Eighteen minutes after shock.

Record 7.—Twenty-six minutes after shock; blood sugar 30 mg. per hundred cubic centimeters.

In this experiment remarkable recovery of the electroencephalogram and the behavior occurred, in spite of continued coma levels of the blood sugar. The blood sugar levels were determined according to the method of Shaffer and Hartman.

interesting in view of the recovery obtained with electrically induced convulsions. An example of this reaction is presented in figure 5, in which is shown the effect on the electroencephalogram not only of the gradual development of hypoglycemia but of the convulsions which followed the coma. Record 9 shows that immediately after the period of convulsions, which lasted about four minutes, the electroencephalogram was almost normal. During this time the animal was quiet and showed some clinical recovery. Thereafter the convulsions reappeared; the

9. This type was regularly observed by us in rats subjected to a low oxygen tension by lowering of the barometric pressure to 200 mm. of mercury.

10. Bremer, F.: Cerveau "isolé" et physiologie du sommeil, *Compt. rend. Soc. de biol.* **118**:1235-1241, 1935; Quelques propriétés de l'activité électrique du cortex cérébral "isolé," *ibid.* **118**:1241-1244, 1935.

alpha potentials were greatly reduced in size; slow waves and spikes appeared, and, finally, the electrical activity disappeared almost completely. The animal died shortly afterward. This experiment shows that insulin convulsions may, to a certain extent, temporarily induce recovery, although the effect was never as distinct and lasting as that in hypoglycemic rats subjected to convulsions induced by electric shock.

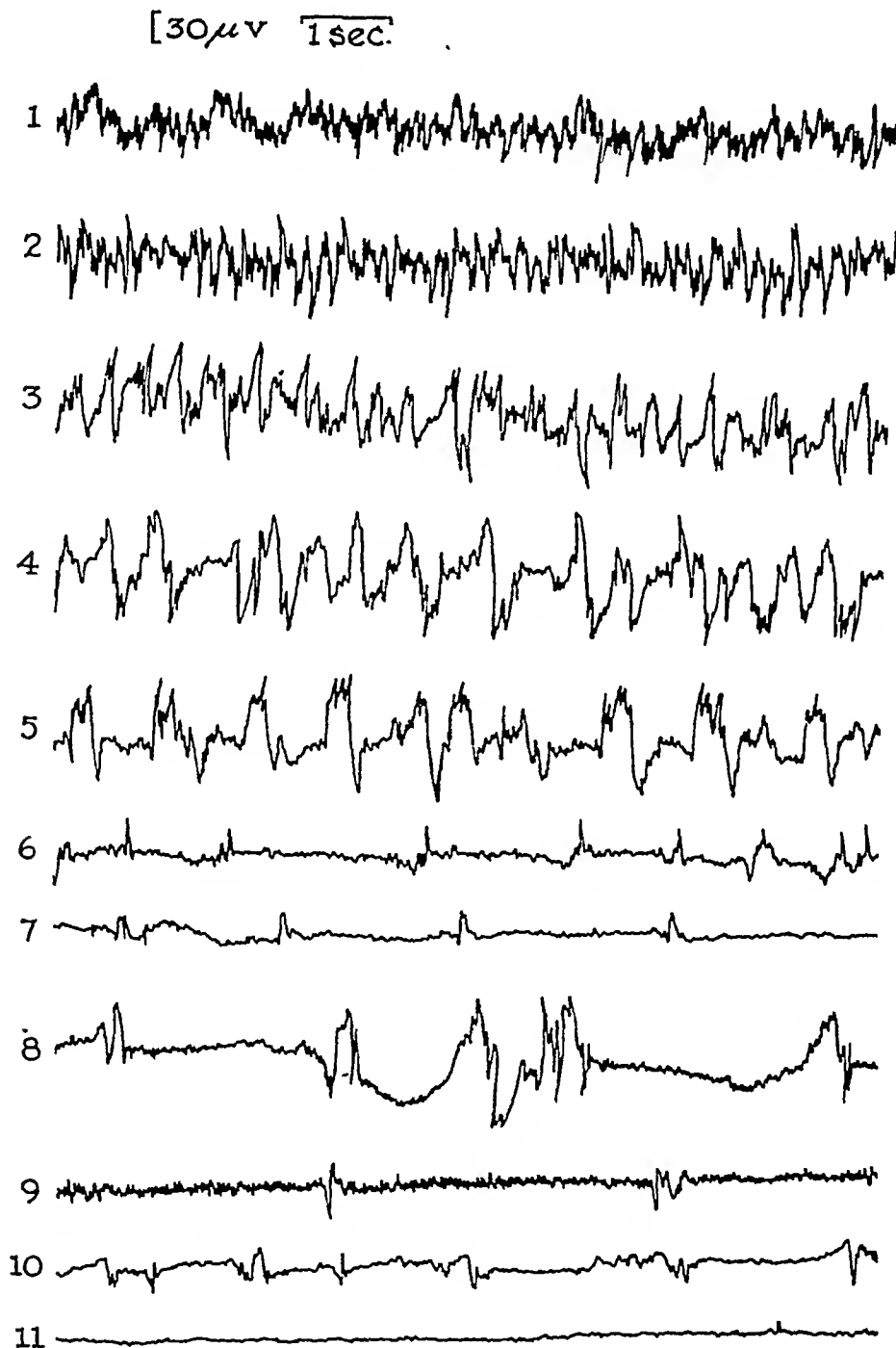


Fig. 5.—Effect of spontaneous convulsions on the electroencephalogram of an adrenomedullated rat.

Record 1.—Control; blood sugar 110 mg. per hundred cubic centimeters.

1: 17 p. m.: Subcutaneous injection of 2 units of insulin per kilogram of body weight.

Record 2.—2 p. m.: Blood sugar 82 mg. per hundred cubic centimeters.

Record 3.—2: 19 p. m.: Animal insensitive to pain; no righting reflex; blood sugar 52 mg. per hundred cubic centimeters.

Record 4.—2: 31 p. m.: Deep coma; blood sugar

53 mg. per hundred cubic centimeters.

Record 5.—2: 37 p. m.: Deep coma.

Record 6.—2: 38 p. m.: Some convulsive jerks.

Record 7.—2: 42 p. m.: Intermittent clonic convulsions.

Record 8.—2: 42 p. m.: Tonic convulsions.

Record 9.—2: 43 p. m.: No convulsions; electroencephalogram nearly normal.

Record 10.—2: 50 p. m.: Further convulsions.

Record 11.—2: 55 p. m.: Animal died.

The question arises as to the means by which cortical function may be restored by electrically induced convulsions in spite of the fact that hypoglycemia remains unchanged. Two fundamental possibilities must be considered. It may be assumed that electrically induced convulsions may set up impulses in the central nervous system which greatly alter the excitability of the cortex and the rest of the brain. Or, electric shock may act on sympathetic centers in the hypothalamus and the medulla and thus improve circulatory conditions in the brain. It is conceivable that in either case considerable improvement in cortical function may occur in spite of the persistence of low blood sugar levels which prior to the electric shock regularly produced coma. Since previous experiments have shown that electric shock, as well as hypoglycemia, alters the excitability of the autonomic centers¹¹ and increases the concentration of epinephrine in the blood, it may be thought that the centers involved in this reaction may stimulate the cortex and restore its excitability.

That afferent stimuli may alter cortical activity in hypoglycemic coma was shown by Moruzzi.¹² He demonstrated that even after spontaneous cortical activity had disappeared during hypoglycemia potentials could be evoked by afferent stimuli. It is unlikely, however, that stimuli of this type could ever be potent enough to restore normal cortical potentials for many minutes in spite of continued hypoglycemia. It seems more likely, therefore, that the restoration of cortical function is associated with improvement in the utilization of oxygen by the brain in spite of persistent hypoglycemia.

Since the experiments were performed in the presence of relatively large quantities of insulin in the blood and since it has been shown that the utilization of oxygen is directly related to both the blood sugar level and the amount of insulin circulating in the blood,¹³ it may be assumed that in insulin hypoglycemia optimal conditions exist for the utilization of the small amounts of dextrose which are available at the coma-producing blood sugar level. It is unlikely, therefore, that stimulation of the sympathetic system would further improve the utilization of dextrose. A discussion of the possible role of epinephrine may be omitted since the experiments were performed on adrenodemedullated animals. Inasmuch as the dextrose uptake of the brain, other conditions being equal, depends on the amount of blood flowing through the brain per unit of time, the possibility must now be considered that the blood flow through the brain is increased after electric shock. Although actual determinations of the influence of electric shock on the blood flow in hypoglycemic rats could not be made, studies on the pulse rate under these conditions reveal a striking, and as we believe significant, change in sympathetic excitability, which is bound to affect the excitability of the brain.

A series of experiments were performed on normal, adrenodemedullated and adrenalectomized rats, to determine the effect of electric shock on the pulse rate. Electrocardiographic records were obtained by the same amplifier which was used for the recording of the electroencephalograms. The effects were similar in all

11. For full discussion of the literature, see Gellhorn, E.: *Autonomic Regulations: Their Significance for Physiology, Psychology and Neuro-Psychiatry*, New York, Interscience Publishers, Inc., 1943.

12. Moruzzi, G.: *Étude de l'activité électrique de l'écorce cérébrale dans l'hypoglycémie insulinaire et dans différentes conditions modifiant le métabolisme des centres*, Arch. internat. de physiol. 48:45-101, 1939.

13. Evans, C. L.; Grande, F., and Hsu, F. Y.: The Glucose and Lactate Consumption of the Dog's Heart, Quart. J. Exper. Physiol. 24:347-363, 1935. Soskin, S., and Levine, R.: A Relationship Between the Blood Sugar Level and the Rate of Sugar Utilization, Affecting the Theories of Diabetes, Am. J. Physiol. 120:761-770, 1937.

three groups and consisted of a rapid fall in pulse rate for one or two minutes, after which the pulse frequency was gradually restored to the original level or to a rate slightly below it. The practical identity of the results obtained on normal and on adrenalectomized rats indicates clearly that the secretion of epinephrine is not a factor in the alteration of the pulse rate under our experimental conditions.

Experiments were then performed in which the effect of electric shock on the pulse rate was observed in rats in hypoglycemic coma. The results, which are seen in figure 6, show that whereas the pulse rate decreases temporarily as a result of electric shock in normal rats, it increases in hypoglycemic animals subjected to electric shock. It is worthy of note that although hypoglycemic rats show a decreased frequency of the heart as compared with the frequency at a normal blood sugar level, the heart rate of such animals after electric shock is distinctly above the minimum seen in normal rats. The failure of hypoglycemic rats to respond to electric shock with a fall in heart rate is therefore due not to an already maximal excitation of the vagus nerve but to a change in autonomic balance and a decided increase in sympathetic excitability, which is present even at the late stage of hypoglycemia, at which apparently parasympathetic discharges

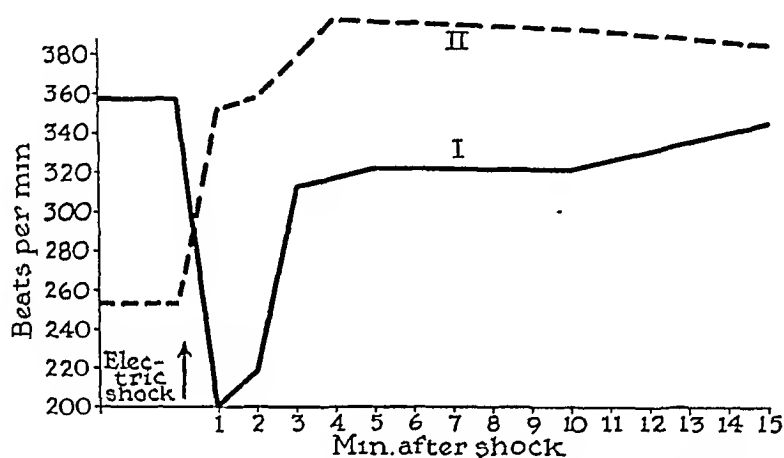


Fig. 6.—Effect of electric shock on the pulse rate of adrenalectomized rats both with the blood sugar at a normal level and during insulin coma. Each graph is the average results obtained on 6 rats. The solid line indicates values for adrenalectomized rats with normal blood sugar levels; the broken line, the values for adrenalectomized rats in insulin coma.

become prominent. The increased sympathetic excitability is also apparent from the fact that the pulse rate of hypoglycemic animals after electric shock rises even above the normal pulse rate of untreated animals.

It is obvious that the considerable increase in pulse rate which persists for some time after the administration of electric shock to hypoglycemic animals must be an important factor in the increase of the rate at which the blood flows through the brain. This reaction, possibly in conjunction with other sympathetic responses (rise in blood pressure through vasoconstriction), appears to be the main cause of the recovery of cerebral function in hypoglycemic animals subjected to electric shock.

COMMENT

It was pointed out in 1938 by one of us (E. G.)^{2a} that the feature common to the various forms of "shock therapy" is their excitation of the sympathetic centers. This effect appears to be of significance, since schizophrenic patients show a diminished response to stimuli involving reactions of the sympathetic centers and exhibit improvement in this response when the treatment results in definite

benefit.¹¹ In the light of these observations and interpretations, it is of interest to point out that a combination of electric shock and insulin coma produces greatly increased excitation of sympathetic centers and, according to some authors,¹⁴ gives better therapeutic results. The fact demonstrated in these experiments that electric shock combats insulin coma effectively, even in adrenomedullated rats, in which the blood sugar level is not raised, has been interpreted to mean that cerebral circulation is improved after electric shock. In support of this interpretation is our experimental observation that electric shock increases the pulse rate (and possibly the blood pressure) when applied to adrenomedullated animals with hypoglycemia, although it slows the heart rate when applied to rats with a normal blood sugar.

It is further worthy of note that rats kept in insulin coma for one hour fail to recover after administration of an adequate amount of dextrose, although the blood sugar rises. On the other hand, rats may be kept at the same coma level for the same period without harm provided that they are "treated" with electric shock. Not only do these animals show temporary recovery after electric shock, but they present no signs of permanent impairment.

It was mentioned earlier that the occurrence of spontaneous convulsions during hypoglycemia leads, in some instances, to temporary improvement of cerebral functions. Apparently, sympathetic discharges elicited during spontaneous convulsions improve the circulation in the brain for a short time.

Our investigations throw a new light on the effect of anoxia when induced during insulin hypoglycemia. McQuarrie and collaborators¹⁵ observed in the dog, and Gellhorn, Packer and Feldman¹⁶ confirmed for the rabbit, that injection of convulsant doses of insulin failed to induce either coma or convulsions when the animal was subjected to a prolonged period of anoxia, although the blood sugar level was even lower than that in control animals given injections of insulin alone. The failure of the blood sugar to rise in response to anoxia was adequately explained by the observation that epinephrine loses its glycogenolytic effect on the liver after prolonged anoxia.¹⁷ It was not explained, however, why under the combined influence of anoxia and hypoglycemia the animals remained normal although the blood sugar was at a coma level.

Since it has been shown in the present paper that hypoglycemic coma may be terminated, without alteration of the blood sugar level, by a procedure (electric shock) which, through excitation of the sympathetic nervous system, improves the circulation in the brain, it is of interest to inquire whether this mechanism may not be responsible for the absence of hypoglycemic symptoms in animals subjected to insulin hypoglycemia and prolonged anoxia. This explanation seems, indeed, to be valid, since the pressor effect induced by anoxia increases with the fall in blood sugar (Gellhorn, Ingraham and Moldavsky^{2b}). We have evidence, therefore, that anoxia, as well as electric shock, causes increased sympathetic discharges during hypoglycemia, which will improve the circulation in the brain through increasing the systemic blood pressure. In experiments in which animals are

14. Jessner, L., and Ryan, V. G.: *Shock Treatment in Psychiatry*, New York, Grune & Stratton, Inc., 1941.

15. McQuarrie, I.; Ziegler, M. R.; Stone, W. E.; Wangenstein, O. H., and Dennis, C.: Mechanism of Insulin Convulsions: III. Effects of Varying Partial Pressures of Atmospheric Gases After Adrenalectomy, *Proc. Soc. Exper. Biol. & Med.* **42**:513-514, 1939.

16. Gellhorn, E.; Packer, A., and Feldman, J.: Studies on Hypoglycemic and Anoxic Convulsions, *Am. J. Physiol.* **130**:261-267, 1940.

17. Gellhorn, E., and Packer, A.: Studies on Hypoglycemia and Anoxia, *Am. J. Physiol.* **129**:610-617, 1940.

subjected to insulin hypoglycemia and prolonged anoxia, the greatly increased sensitivity of the vasomotor center to anoxia effectively counteracts the influence of hypoglycemia, while in the experiments described in this paper the hypoglycemic action seems to be offset by electric shock through the rise in pulse rate, which is probably attended by similar changes in cardiac output and blood pressure.

It may, therefore, be said that under the influence of increased sympathetic discharges, elicited either by anoxia or by electric shock, the functions of the brain may remain normal in spite of coma-producing levels of the blood sugar.

SUMMARY

Electric shock (40 volts and 30 milliamperes) applied for one or two seconds to unanesthetized rats causes tonic-clonic convulsions, followed by a period of "catatonia" and gradual recovery. After the potentials associated with convulsions the electroencephalogram shows a period of silence. Thereafter delta potentials appear, while alpha potentials either are reduced in size or are absent. Gradually the alpha potentials recover and the delta potentials disappear.

Hypoglycemia induced by the injection of 5 units of insulin per kilogram of body weight leads to coma and typical changes in the electroencephalogram (delta potentials and reduction or absence of alpha potentials). Animals not given injections of dextrose die in coma or convulsions. If hypoglycemia is maintained by administration of small amounts of dextrose, the duration of the coma may be prolonged, but the animals fail to recover on the injection of adequate amounts of dextrose in spite of hyperglycemia.

After electric shock has been applied to adrenodemedullated rats in a hypoglycemic state, a surprising recovery is observed. The coma disappears; the animals show normal behavior, and the electroencephalogram returns to normal in spite of the fact that the blood sugar remains unchanged at its coma level. These results, suggesting increased utilization of dextrose, appear to be due to an increased blood flow through the brain. This interpretation is supported by the fact that the pulse rate is increased by electric shock in the hypoglycemic animal, whereas it is decreased in the normal animal. The experiments give additional proof of the greatly increased excitability of the sympathetic centers in hypoglycemia.

The theoretic and practical consequences of these observations are discussed.

1853 West Polk Street.

STUDIES ON THE CORPUS CALLOSUM

IX. RELATIONSHIP OF THE GRASP REFLEX TO SECTION OF THE CORPUS CALLOSUM

ANDREW J. AKELAITIS, M.D.

WILFORD A. RISTEEN, M.D.

AND

WILLIAM P. VAN WAGENEN, M.D.

ROCHESTER, N. Y.

The grasp reflex is a flexor response of the digits to stimulation of the palm or to stretching of the flexor tendons of the hand. It occurs normally in infants and pathologically in adults with lesions of the frontal lobe predominantly. Schuster and Casper¹ attempted to explain this phenomenon as an absence or interruption of the inhibitory pathway which normally suppresses reflex grasping. This hypothetic pathway is bilateral in its origin and arises from the medial surface of the superior frontal convolution and the gyrus cinguli. The fibers pass backward to the level of the central area, some passing directly to the prerolandic area of the homolateral hemisphere and others crossing in the corpus callosum to terminate in the central area of the opposite side. Schuster and Casper¹ and Schuster and Pinéas² reported the occurrence of forced grasping in patients with large tumors of the corpus callosum. Wilson³ spoke of the occasional appearance of forced innervation in cases of callosal lesions. Richter and Hines⁴ and Kennard and Watts⁵ were unable to find forced grasping or groping after section of the corpus callosum in monkeys.

The present paper is concerned with the study of 30 cases of epilepsy in which the corpus callosum was partially or completely sectioned.⁶ In 5 of these severe hemiplegia was present and the cases could not be used in this study. In 22 of the remaining 25 cases the grasp reflex was absent after operation. The 3 cases in which a transient unilateral grasp reflex was present after operation are reported in detail.

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From the Department of Medicine, Division of Psychiatry (Dr. Akelaitis), and the Department of Surgery, Division of Neurosurgery (Drs. Risteen and Van Wagenen), University of Rochester School of Medicine and Dentistry, and the Clinics of the Strong Memorial and Rochester Municipal Hospitals.

1. Schuster, P., and Casper, J.: *Zwangsgreifen und Stirnhirn*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **129**:739, 1930.

2. Schuster, P., and Pinéas, H.: *Weitere Beobachtungen über Zwangsgreifen und Nachgreifen und deren Beziehungen zu ähnlichen Bewegungsstörungen*, *Deutsche Ztschr. f. Nervenheilk.* **91**:16, 1926.

3. Wilson, S. A. K.: *A Contribution to the Study of Apraxia, with a Review of the Literature*, *Brain* **31**:164, 1908.

4. Richter, C. P., and Hines, M.: *The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions*, *A. Research Nerv. & Ment. Dis., Proc.* (1932) **13**:211, 1934.

5. Kennard, M. A., and Watts, J. W.: *The Effect of Section of the Corpus Callosum on the Motor Performance of Monkeys*, *J. Nerv. & Ment. Dis.* **79**:159, 1934.

6. Van Wagenen, W. P., and Herren, R. Y.: *Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack*, *Arch. Neurol. & Psychiat.* **44**:740 (Oct.) 1940.

REPORT OF CASES⁷

CASE 1 (case 15⁸).—E. H., a stock clerk, married, aged 51, was admitted to the Strong Memorial Hospital on March 26, 1940. For the past four years he had been subject periodically to grand mal seizures, which usually occurred in series (status epilepticus). One week before admission he began to have seizures and at the time of admission was having an attack every fifteen minutes. Each seizure began with a cry, adverse movements to the left, with the eyes in left conjugate deviation, and tonic movements of the left arm, followed by generalized muscular twitchings. The seizure lasted usually about three minutes, and in the intervals he was paraphasic and confused. The attacks ceased the next day, but paraphasia continued until March 30. He remained confused and showed psychobiologically a reaction typical of a patient with diffuse organic disease of the brain, that is, disturbances in the sensorium, mental capacity and intellect. The physical and neurologic status was normal on April 2. He was right eyed, right handed and right footed.

Ventriculograms taken in 1937 and on March 28, 1940 revealed nothing abnormal.

Operation.—On April 6 the corpus callosum was sectioned completely except possibly for a few fibers in the tip of the splenium. A large vein entering the longitudinal sinus from the right frontal lobe was ligated. The cortex showed considerable atrophy, especially toward the frontal pole. Microscopic study of a piece (1 cm. in diameter) of cortex from area 9 of Brodmann on the right side disclosed diffuse loss of nerve cells throughout the third, fifth and sixth layers, and with Cajal's silver stain numerous argentophilic bodies were evident within nerve cells and lying free in the parenchyma. No senile plaques were visible in Braunnühl preparations. These changes were suggestive of Pick's atrophy.

Postoperative Course.—The postoperative course was stormy and complicated. For the first two days the patient was semicomatose, and on the fourth postoperative day the left hand grip was very weak and the left leg limp. During the first week he rarely moved the left side of his body. Although the tendon reflexes were active and equal bilaterally, plantar stimulation resulted in a dorsal extensor response of the left big toe. Sensory studies were unsatisfactory because of the patient's apprehensiveness and confusion, but it was evident after repeated examinations that hyperesthesia prevailed over the left side.

Ten days after operation the neurologic status was normal except for astereognosis and an ideokinetic type of dyspraxia in the left hand. Definite forced innervation and occasional groping were observed in the left hand. The patient was unable to write with a pencil placed in his left hand. When he was requested to transfer the pencil from the left hand to the right, he grasped the pencil with the right hand but could not take it out of his tightly clenched left fist. Finally, he succeeded in pulling the pencil out but proceeded to make repeated groping movements with the left hand. When he was asked to transfer the pencil from the right hand to the left, no evidence of forced innervation in the right hand occurred. When he was asked to squeeze hands, the pressure in the left hand seemed episodic, but he released the grip when told to do so. Asked to make a fist with the left hand, he was unable to do so, even though he imitatively clenched his right hand repeatedly. If the right hand was not restrained, he invariably placed his right forefinger against the palm of the left hand, and the fingers closed adequately to form a fist. He had no difficulty in removing the forefinger, and no forced innervation was observed when the examiner's fingers were used as a stimulus. However, if a pencil or other inanimate object was employed as a stimulus, forced innervation became evident, and the more one attempted to pull the object out, the greater the grasp became. Stroking the surface of the dorsum of the hand simultaneously with the palmar stimulation or after the grasping had occurred had no effect on the grasp. The only successful method of retrieving the grasped object was to distract the patient's attention by conversation or the performance of some task with his right hand. He easily acquired a "catastrophe reaction,"⁹ and when he was fatigued he was apt to become confused. Later in the morning he showed no difficulty whatever in eating bread from his left hand. The forced innervation and occasional groping movements in the left hand were present sporadically for the following ten days, associated with astereognosis and tactile alexia. The former was invariably precipitated or aggravated by confusion and fatigue.

7. These cases have been reported in greater detail in a previous paper.⁸ The case number in parentheses will identify the case.

8. Akelaitis, A. J.; Risteen, W. A.; Herren, R. Y., and Van Wagenen, W. P.: Studies on the Corpus Callosum: III. A Contribution to the Study of Dyspraxia and Apraxia Following Partial and Complete Section of the Corpus Callosum, Arch. Neurol. & Psychiat. 47:971 (June) 1942.

9. A term employed by Goldstein (Goldstein, K.: The Organism, New York, American Book Company, 1939) to denote the disordered responses in subjects undergoing study.

Beginning on April 30 and continuing for three days, numerous right-sided seizures occurred, which left him with right hemiplegia and aphasia. At this time no forced innervation or groping was noted in the left hand, and he was able to eat with this hand fairly well. The aphasia and hemiplegia cleared in one week, and a slight tendency to hold on to objects with the right hand was observed; the left hand showed no forced innervation. He left the hospital on May 9. When he was seen in August 1940, the neurologic status was normal except for dysdiadokokinesis in the left hand when the hands were tested simultaneously and questionable hypesthesia (tactile and vibration senses) over the right lower extremity. The psychiatric status showed disturbances in calculation and defects in recent memory and immediate retention. These defects were no more pronounced than before operation.

CASE 2 (case 16^s).—C. S., a 15 year old girl of borderline intelligence, was admitted to the Strong Memorial Hospital on Jan. 4, 1940. Left hemiplegia developed during an attack of "encephalitis" at the age of 15 months. As a result of physical therapy and reeducation she was able to knit and sew fairly well, but had never succeeded at typing or piano playing because of the awkwardness in the left hand. Petit mal seizures began at the age of 5 years, and grand mal seizures had been present since the age of 11 years. The physical status was good. Neurologic examination disclosed residual left hemiplegia, with some atrophy, slight spasticity, an infrequent Babinski response and occasional athetoid movements on the left side. Careful sensory studies revealed a normal status. The Binet level was 12 years and 4 months (intelligence quotient 81). Laterality studies revealed left ocular dominance, right handedness and right footedness.

Operation.—On January 22 a right frontoparietal craniotomy was performed, and the corpus callosum was completely sectioned. The cortex of the right hemisphere showed a moderate degree of atrophy.

Course.—For the first four days the left side was immobile and the hand grip weak, the patient complained of numbness and hypesthesia to all modalities was evident on the left side. On the fifth postoperative day a striking grasp reflex appeared in the left hand when the examiner attempted to raise her by the hands. However, stroking of the palm with the finger or pencil produced no grasping, but tension on the flexor tendons invariably did. She showed difficulty in touching her nose or scratching the back of her neck with the left hand on request but did so without any effort when these areas were tickled. She showed awkwardness in any requested movement with her left hand, and definite ideokinetic dyspraxia in this hand was noted. Sensory studies revealed disturbances of all modalities over the left side. Nine days after operation forced innervation was marked in the left hand; frequently, when she tried to release her grasp she gripped the examiner's hand with greater intensity. Usually she loosened her grip when distracted. However, stretching of the flexor tendons of the left hand did not result in grasping. It was frequently observed that she fingered the call string easily and showed no tendency to forced innervation in this activity. This forced innervation, along with sensory disturbances, continued to exist until her discharge, on March 4, 1940. However, she could use a fork in her left hand while eating and manipulated the wheel chair with both hands without difficulty.

When she was seen in August 1940 (seven months after operation) no forced innervation was evident, and she could write with her left hand. Sensory disturbances prevailed in the left arm but were less pronounced than during her early postoperative stay in the hospital.

CASE 3 (case 14^s).—M. L. P., a 10 year old white girl, was admitted to the Strong Memorial Hospital on March 12, 1940. Psychobiologic development was normal up to the age of 3 years, when she was struck over the left parietal region by a falling object. Two weeks later status epilepticus developed, and on her awakening, aphasia, right hemiplegia and external strabismus were observed. The strabismus improved, and she talked again after two months. The hemiplegia improved, and on admission she exhibited a slightly spastic gait and some clumsiness in her right hand. Six months before admission she began to have petit mal attacks.

The physical status was good. Neurologic examination revealed defective vision in the left eye (3/60), right homonymous hemiamblyopia, left external strabismus and residua of right hemiplegia, with increased motor tonus, exaggerated deep reflexes and a positive Babinski sign on the right side. The sensory status, including two point discrimination and stereognosis, was normal. She performed various tasks surprisingly well with her right hand but could not shuffle playing cards. Laterality studies disclosed right ocular dominance, left handedness and left footedness.

Laboratory Studies.—An encephalogram disclosed hydrocephalus of the left lateral ventricle and shifting of all ventricular structures to the left. Electroencephalograms showed 6 per second delta waves, with an amplitude of 15 to 20 microvolts, over the left parietal region and occasional delta waves, with an amplitude of less than 10 microvolts, from the right frontal and temporocentral regions.

Operation.—On March 29, 1940 a right frontoparietal craniotomy was performed and the corpus callosum sectioned almost completely except for the posterior 0.5 cm. The left fornix was divided.

Course.—On the patient's awakening from the anesthesia bilateral grasp reflexes were observed. The following day (March 30) motor strength was good bilaterally, and a grasp reflex was elicited only in the right hand. She tended to hold onto the examiner's hand or an inanimate object with her right hand. When she was asked to squeeze hands, the pressure in the right hand was episodic, and when she was asked to release her grip, not infrequently she would continue to squeeze with greater force. Stroking of the dorsal tendons had no effect on the degree of forced innervation. Generally distraction of the patient's attention resulted in immediate relaxation of the right hand grip. Stretching of the flexor tendons did not result in grasping. This forced innervation in the right hand was present irregularly for one month after operation. On April 4 she wrote with either hand, but perseveration was observed in the left hand. Perseveration continued irregularly in her conversation and in the performance of tasks for one month after operation. Throughout this period she handled a fork in her right hand as efficiently as before operation and manipulated her wheel chair successfully. In spontaneous tasks forced innervation never seemed to be evident in the right hand.

One month after operation and at the last examination (Oct. 7, 1941) no evidence of forced innervation in the right hand was elicited. Astereognosis has continued to exist in the right hand, even though two point discrimination and interpretation of skin writing remain intact.

COMMENT

The common aspects of all 3 cases should be discussed first. In each case evidence of cerebral damage was present before operation. In case 1 clinical and anatomic changes were suggestive of Pick's atrophy. In case 2 there was a history of encephalitis at the age of 15 months, with the development of left hemiplegia. Clinically the patient presented signs of residual hemiplegia, and at operation the cortex of the right hemisphere showed a moderate degree of atrophy. In case 3 right hemiplegia developed after status epilepticus and a head injury at the age of 3 years, and at the time of admission clinical and laboratory evidence pointed to a moderately extensive lesion of the left hemisphere. The interesting feature in cases 2 and 3 was the predominant involvement of the anterior portion of the hemisphere unilaterally. In 2 cases reported elsewhere (cases 1 and 2¹⁰) evidence of unilateral damage to the posterior portion of the hemisphere was presented, but a grasp reflex did not follow complete section of the corpus callosum. In case 1 in the present study the atrophy was apparently diffuse and progressive and presumably involved both hemispheres. At operation, so far as the field of operation allowed visual inspection, the atrophy was most evident toward the frontal pole. From this discussion it is evident that the limb contralateral to the damaged hemisphere showed no grasping reflex or forced innervation at the time of operation, the response having been suppressed by the inhibitory pathway in the corpus callosum arising from the opposite, or intact, hemisphere. After complete section of the corpus callosum, as in case 2, or almost complete section, as in cases 1 and 3, this inhibitory pathway was destroyed and the reflex grasping released. These observations tend to substantiate the hypothesis of Schuster and Casper.¹

The possibility of added damage at operation to an already impaired hemisphere must next be considered. In cases 1 and 2 the craniotomy was performed contralateral to the extremity which showed the grasp reflex. The early postoperative clinical findings further suggested that added injury may have occurred. For example, in case 1 there were evidence of hyperesthesia and a positive Babinski

10. Akelaitis, A. J.: Studies on the Corpus Callosum: V. Homonymous Hemiambyopia (Homonymous Defects for Color, Object and Letter Recognition) Before and After Section of the Corpus Callosum, *Arch. Neurol. & Psychiat.* 48:108 (July) 1942.

sign on the left side, which were temporary, and in case 2 sensory changes, consisting of hypesthesias and paresthesias in the left arm, were associated with increased motor paresis. These signs strongly suggest the presence of added damage to the right hemisphere in both cases. In 3 cases reported elsewhere (cases 11, 12 and 13⁸) in which clinical and/or anatomic evidence of operative damage to the anterior portion of the hemisphere was present, paresis and a kinetic type of dyspraxia occurred, but no grasping reflex was ever noted in the contralateral limb. Of course, this comparison is of questionable value, in view of the fact that in the 2 cases here reported the injury may have been slighter or may have involved different cortical areas. However, in case 3 of the present series, in which a right craniotomy was performed, the grasp reflex occurred in the homolateral (right) hand, and not in the left, after operation. It is probable that the appearance of the grasp reflex in the subordinate hand in all 3 cases resulted primarily from the section of the corpus callosum. These observations are contradictory to the experimental results of Kennard and Watts,⁹ who not only did not find forced grasping when the corpus callosum was sectioned in the intact macaque, but showed that in a unilateral or bilateral premotor preparation in which forced grasping had disappeared, section of the corpus callosum did not cause the symptom to return.

The difficulty in the relaxation of contracted muscles was accompanied by dyspraxic manifestations in each case. In cases 1 and 2 an ideokinetic type of dyspraxia prevailed, whereas in case 3 the dyspraxia was kinetic. In all 3 cases difficulty was experienced in opening the clenched fist when it was empty. Wilson and Walshe¹¹ and Walshe and Robertson¹² stressed this point, in the belief that the factor of apraxia is of utmost importance in this phenomenon. In case 1 a peculiar differentiation was observed. The patient would continue to hold on to any inanimate object placed in his left hand when he was requested to loosen his grasp on it, and any effort to pull it out forcibly resulted in increased clenching. Yet he had no difficulty in releasing his grip when the examiner's finger was placed in the left palm, and even learned to make a fist with his left hand by using his right index finger as a palmar stimulus. This phenomenon surely suggests a higher type of reaction than would occur in purely reflex behavior. In cases 2 and 3 no such differentiation in reactions occurred.

In all 3 cases there was profound difficulty in making a fist voluntarily. In cases 1 and 2 the patient made repeated fists with the normal hand, looking from the intact hand to the dyspraxic hand and expressing perplexity and irritation over the inability to do with the left hand what could be done so easily with the right. In all probability this disturbance was a manifestation of dyspraxia.

A third interesting point in the behavior of the three patients was that in ordinary, more or less spontaneous acts, such as eating or manipulating the wheel chair, no forced innervation occurred in the "defective" hand so as to interfere with these activities. This behavior further suggests the presence of dyspraxia. Attention probably plays a definite, but variable, role in this phenomenon, as stressed by several workers, especially Wilson and Walshe¹¹ and Schlesinger.¹³ Schlesinger mentioned Fulton's observations that forced grasping disappeared in some of his animals at feeding time.

11. Wilson, S. A. K., and Walshe, F. M. R.: The Phenomenon of "Tonic Innervation" and Its Relation to Motor Apraxia, *Brain* **37**:199, 1914.

12. Walshe, F. M. R., and Robertson, E. G.: Observations upon the Form and Nature of the "Grasping" Movements and "Tonic Innervation" Seen in Certain Cases of Lesion of the Frontal Lobe, *Brain* **56**:40, 1933.

13. Schlesinger, B.: Forced Grasping and Disturbances of Attention, *J. Ment. Sc.* **86**:827, 1940.

SUMMARY

In 22 cases of epilepsy in which the frontal lobes were relatively intact, partial and complete section of the corpus callosum did not result in forced innervation or forced grasping.

In 3 cases of chronic unilateral lesions involving the anterior portion of the hemisphere, partial or complete section of the corpus callosum resulted in the temporary appearance of forced grasping in the contralateral hand. This was associated with an ideokinetic dyspraxia in 2 cases and with exaggeration of a preoperative kinetic dyspraxia in the third case.

CONCLUSIONS

In the presence of a chronic lesion involving the frontal lobe, grasping movements can be temporarily released in the contralateral hand after section of the corpus callosum.

There may be a close relation between forced grasping and dyspraxia.

260 Crittenden Boulevard.

EXPERIMENTAL SWELLING OF THE BRAIN

S. OBRADOR

AND

J. PI-SUÑER

MEXICO, MEXICO

The occurrence of local swelling or edema of the cerebral cortex following a lesion is well known. Aside from this localized disturbance, generalized swelling of the brain is occasionally observed in the course of some neurosurgical procedure, such as operation on the pituitary region, and may also be produced experimentally by lesions of the midbrain (Le Beau and Bonvallet¹). We have studied this type of experimental swelling of the brain following lesions of the floor of the fourth ventricle and the medulla.

METHOD

Sixty-six adult dogs were used in this series. All the experiments were carried out with the animals under anesthesia induced with soluble pentobarbital U. S. P. To observe the volume of the brain one or two trephine windows (1 to 1.5 cm. in diameter) were made in the parietal region, and the dura was opened. Craniotomy was made in the region of the posterior fossa to expose the cerebellum, the fourth ventricle and the medulla. In some experiments the cerebellum was completely removed in order to uncover the region of the fourth ventricle. Compression or lesions at different levels of the fourth ventricle and medulla were made. In addition to observations on the brain volume, made through the cranial windows, records of the blood pressure and respiration were taken.

To study the cerebral circulation, samples of arterial and cerebral venous blood were taken simultaneously from the femoral artery and the external jugular vein respectively, and their oxygen contents were determined by the Van Slyke method.

The water content of the cerebral tissue was determined by drying small samples of gray and white matter for several days in an oven at 60 C. until a constant weight was obtained. Separation of the gray and the white matter was carried out immediately after removal of the brain.

All the experiments were acute and lasted only one to three hours.

RESULTS

Vasomotor Responses and Cerebral Swelling.—It is already well known that in the medulla and the fourth ventricle there are centers or mechanisms that participate in the regulation of the level of the blood pressure and that through these regions run descending vasomotor pathways from higher centers. In a previous publication² we reviewed the literature concerning the localization of vasomotor responses in the region of the fourth ventricle.

Compression, lesion or complete section of the floor of the fourth ventricle gives rise to vasomotor responses and usually to slowing down or complete cessation of respiration. The type of response varies with the level involved. Usually localized compression or section at the lower end of the floor of the fourth ventricle gives rise to a decided increase in blood pressure. Sometimes there appears the opposite effect, i. e., a fall in blood pressure; this is especially

From the Laboratorio de Estudios Médicos y Biológicos, Facultad de Medicina de México.

1. Le Beau, J., and Bonvallet, M.: Oedeme aigü du cerveau par lesion du tronc cerebral, *Compt. rend. Soc. de biol.* **127**:126, 1938.

2. Obrador, S., and Pi-Suñer, J.: Respuestas vasomotoras por excitación mecánica del suelo del IV ventrículo, *Ciencia* **3**:63, 1942.

frequent when the section is through the upper part of the floor of the fourth ventricle. In other cases the vasomotor responses are mixed, with an initial fall in blood pressure and a secondary rise.

A lesion in the lower end of the floor of the fourth ventricle gives rise usually to swelling of the cerebral cortex. Sometimes the swelling appears quickly, and in a few seconds there is herniation of the cortex through the observation window. In other experiments the development is slower and less pronounced; there are on the whole great differences in the degree of presentation of the cerebral swelling.

TABLE 1.—*Oxygen Content of Arterial and Cerebral Venous Blood Before and After Lesions in the Floor of the Fourth Ventricle*

Experiment Number		Oxygen Content, per Cent		Arteriovenous Difference
		Arterial Blood	Venous Blood	
47	Before the lesion.....	22.40	18.62	3.78
		21.81	17.15	4.66
	After the lesion.....	20.10	19.33	0.77
		20.84	17.62	3.22
48	Before the lesion.....	18.91	17.12	1.79
		19.20	17.51	1.69
	After the lesion.....	19.10	18.00	1.10
		19.81	18.42	1.39
49	Before the lesion.....	19.81	16.74	3.07
		19.52	17.00	2.52
	After the lesion.....	20.10	18.34	1.76
		20.32	18.71	1.61
50	Before the lesion.....	21.50	18.90	2.60
		21.80	19.10	2.70
	After the lesion.....	20.60	18.00	2.60
51	Before the lesion.....	22.60	17.40	5.20
		22.30	17.90	4.40
	After the lesion.....	21.90	18.00	3.90
		22.40	18.40	4.00
52	Before the lesion.....	18.60	15.80	2.80
		19.20	16.00	3.20
	After the lesion.....	19.00	15.90	3.10
53		19.40	16.20	3.20
	Before the lesion.....	21.40	18.60	2.80
		21.00	19.40	1.60
	After the lesion.....	20.80	18.50	2.30
54		21.20	18.70	2.50
	Before the lesion.....	19.30	16.50	2.80
		19.20	16.80	2.40
	After the lesion.....	20.40	17.40	3.00
		20.80	17.90	2.90

The appearance of the swelling generally is simultaneous with the rise in blood pressure, and therefore lesions with a notable vasopressor effect are accompanied more often and regularly by the development of cerebral swelling. However, lesions of the fourth ventricle with a vasopressor effect do not always produce swelling, and sometimes several lesions are necessary for an increase in brain volume to become evident.

Although the presentation of cerebral swelling is usually initiated by an increase in blood pressure, there is not afterward a correlation between the level of the blood pressure and the swelling of the brain. The effects of the lesion on the blood pressure are only temporary, and after several minutes the pressure returns

to its previous level or there is a gradual and steady fall. Generally the swelling of the brain, once it is established, persists for several hours, even if the blood pressure falls to a very low level. There is, therefore, persistent swelling of the brain completely independent of the level of the blood pressure.

Cerebral Circulation and Vascular Factors.—The sudden and rapid development of cerebral swelling following a lesion of the fourth ventricle and the usual simultaneous increase in blood pressure suggest a vascular origin.

We took the arteriovenous difference in oxygen content of the blood as a measurement of the cerebral circulation. All the animals were placed under artificial respiration from the beginning of the experiment to avoid possible changes in oxygen supply. Control samples of arterial and venous blood were taken at an interval of ten to fifteen minutes before the lesion was made. Then we made the lesion or section of the lower part of the fourth ventricle, which produced a vasopressor effect and cerebral swelling. The next samples of blood were taken about ten minutes after the lesion was made and as soon as the blood pressure had fallen to the original level, in order to avoid the secondary effects of the increase of blood pressure on the cerebral circulation. Ten or twenty minutes later the last samples of blood were taken.

The results of these experiments appear in table 1. In the majority of the animals there was no great change in the arteriovenous difference in the oxygen content of the blood. In a few experiments there seemed to be a tendency to a diminution of such arteriovenous difference, indicating a possible increase in blood flow through the brain. However, marked swelling of the brain can appear without any pronounced change in the cerebral circulation, as shown by the method used.

Cerebral swelling after lesions of the fourth ventricle can be produced in animals with ligature of both carotid arteries. Tying off of the carotid arteries does not influence appreciably established swelling of the brain.

The vasopressor drugs, such as epinephrine and solution of posterior pituitary U. S. P., may increase temporarily the cerebral swelling by the effect on the blood pressure. The action of ergotamine tartrate was studied because this drug seems to have a vasoconstrictor action on the cerebral blood vessels (Schmidt and Hendrix³). The intravenous injection of small (0.25 mg.) and repeated doses did not produce any obvious change in the cerebral swelling.

Water Content of Cerebral Tissue.—We determined the fluid content of the brain tissue in animals with lesions of the fourth ventricle, in normal dogs under the same experimental conditions and in animals in which an increase in brain volume was obtained with intravenous injections of great quantities of distilled water (50 to 100 cc. per kilogram of body weight). The results are summarized in table 2. For the control animals, the average figure was 78.4 per cent for the gray matter and 66.9 per cent for the white matter. The dogs with cerebral swelling due to a lesion of the fourth ventricle had an average water content of 79.8 per cent for the gray matter and 68.8 per cent for the white matter, i. e., higher values than those for the normal animals. These figures are identical with the average values of 79.8 and 68.9 per cent for the gray and the white matter respectively of animals given intravenous injections of distilled water. It seems, therefore, that there is a certain increase in the water content of the brain with swelling

3. Schmidt, C. F., and Hendrix, J. P.: The Action of Chemical Substances on Cerebral Blood Vessels, A. Research Nerv. & Ment. Dis., Proc. (1937) 18:229, 1939.

produced by lesion of the fourth ventricle and that this increase is similar in degree to that observed after intravenous injection of large amounts of hypotonic solutions (distilled water).

Effect of Hypertonic Solutions on Cerebral Swelling.—In 9 experiments we tried the effect of intravenous injections of hypertonic solutions of sodium chloride or dextrose. Such a solution decreased the swelling of the brain in 6 animals until it completely disappeared and the normal pulsatory movements of the brain were recovered. In some experiments, after removal of the swelling by a hypertonic solution, production of a new lesion brought back the swelling, which again was removed with another injection of a hypertonic solution.

Histologic Study.—The brains of our dogs with acute swelling of the brain caused by a lesion of the fourth ventricle were studied histologically by Dr. Nieto. No changes in the nerve cells, nerve fibers, myelin sheaths, neuroglia or microglia were observed. The only constant alteration was dilatation of the perivascular spaces. The short duration of these experiments evidently did not allow the development of further morphologic changes.

TABLE 2.—*Water Content of the Gray and the White Matter of the Brain of Dogs Under Different Experimental Conditions*

Experiment Number	Gray Matter		White Matter		Observations
25	77.1	78.1	73.3	Cerebral swelling due to lesion of fourth ventricle in each experimental animal
26	80.2	78.4	70.3	69.1	
27	79.6	78.8	66.4	67.0	
29	80.1	80.5	67.0	61.8	
37	80.5	80.3	70.9	
57	81.4	81.3	69.6	69.6	
58	78.5	78.7	67.2	67.4	
40	80.0	79.8	67.2	67.2	Control, without lesion
46	79.4	79.7	68.2	68.4	
55	76.0	76.0	66.8	
61	78.2	78.2	64.7	66.1	
32	79.2	79.4	69.8	Intravenous injection of distilled water
33	80.4	80.2	70.8	70.8	
56	77.2	80.1	67.8	63.2	
60	81.3	81.1	67.8	67.2	

COMMENT

The swelling of the brain which we observed after lesions of the floor of the fourth ventricle seems to have an initial vascular origin. The lesion produces generalized vasomotor disturbances and, together with them, cerebral swelling. Although we did not see frequently any great changes in the cerebral circulation shortly after the lesion, a vascular factor (vasomotor paralysis or vascular congestion) must be taken into consideration to account for the rapid development of the swelling. Another possible factor is an increase in vascular permeability, but this should act more slowly. Bonvallet and Le Beau⁴ observed that a solution of trypan blue did not pass through the capillaries of the brain with acute swelling due to a lesion of the midbrain. We have also carried out experiments in which we failed to observe diffusion of dyes to the cerebral tissue of brains with acute swelling. An increase in vascular permeability has often been postulated with regard to the pathogenesis of cerebral swelling or edema. Although the method of estimating the water content in small samples of nerve tissue may be

4. Bonvallet, M., and Le Beau, J.: Nouvelles remarques sur l'oedeme aigu experimental du cerveau, *Compt. rend. Soc. de biol.* **131**:1128, 1939.

criticized (Pilcher⁵; Shapiro and Jackson⁶; White, Verlot, Selverstone and Beecher⁷), nevertheless it seems to show an increase of water in the swollen brain, and this can be considered proof of diffusion of fluid through the cerebral capillaries. There is also evidence of an increase of water in the white matter of edematous areas associated with brain tumors (Stewart-Wallace⁸), and we have seen such an increase in the white matter of samples of cerebral tissue collected at operation in cases in which severe swelling of the brain had developed. The dilatation of the perivascular spaces noted in the swollen brains may be due also to diffusion of fluid.

In interpretation of this type of experimental swelling of the brain several factors must be taken into consideration. First, it would seem that vascular disturbances occur because of the lesion in an important region concerned with the vasomotor regulation of the body. These vascular disturbances (increased blood pressure and vasomotor paralysis or stasis) appear to give way to slight changes in the vascular permeability, with an increase in the diffusion of fluids, and eventually there develops swelling independent of the vascular factors (blood pressure, cerebral circulation); that swelling, however, can be reduced by intravenous injection of hypertonic solutions.

SUMMARY

Acute swelling of the brain was produced in dogs by lesions of the lower part of the fourth ventricle and the medulla. This swelling usually appeared with a simultaneous rise in blood pressure, but later the swelling persisted in spite of the fall in blood pressure.

The blood flow through the brain did not show any marked or persistent change in the majority of the experiments.

There was an increase in water content of the gray and the white matter of the swollen brain.

The intravenous injection of hypertonic solutions reduced swelling of the brain in most of the experiments.

The only significant histologic change was dilatation of the perivascular spaces.

The possible explanation of this experimental swelling of the brain induced by lesions of the fourth ventricle is discussed.

5. Pilcher, C.: Experimental Cerebral Trauma: The Fluid Content of the Brain After Trauma to the Head, *Arch. Surg.* **35**:512 (Sept.) 1937.

6. Shapiro, P., and Jackson, H.: Swelling of the Brain in Cases of Injury to the Head, *Arch. Surg.* **38**:443 (March) 1939.

7. White, J. C.; Verlot, M.; Selverstone, B., and Beecher, H. K.: Changes in Brain Volume During Anaesthesia: The Effects of Anoxia and Hypercapnia, *Arch. Surg.* **44**:1 (Jan.) 1942.

8. Stewart-Wallace, A. M.: A Biochemical Study of Cerebral Tissue and of the Changes in Cerebral Oedema, *Brain* **62**:426, 1939.

SCHIZOPHRENIC LANGUAGE

JOHN C. WHITEHORN, M.D.

BALTIMORE

AND

GEORGE KINGSLEY ZIPF, PH.D.

CAMBRIDGE, MASS.

The study of language behavior offers a significant and fascinating approach to the study of mentation in psychotic conditions. In a simple and common sense way, this is recognized in every "mental status" recorded, but the possibilities of more penetrating study are not usually utilized fully, because of obvious difficulties. Curiosity is often blunted, also, by the naive assumption that one says what one means and means what one says, a supposition which leads the listener to believe that the meanings called to his mind by the patient's language are a precise transcript of the patient's meanings—certainly a precarious assumption in the ordinary transaction of asking for road directions, and likely to be an even more precarious guide to the psychotic patient's mentation. Considered simply as behavior, however, speech productions are impeccably objective. Indeed, for the study of behavior, speech has one striking advantage—it can be subdivided into specific and definite acts with great certainty. Words are almost universally recognizable and identifiable as distinct and separate actions. No other type of behavior lends itself so well to unequivocal report and analysis. Furthermore, speech is inherently social or interpersonal, in its historical development and in its learning and primitive use by the person, so that one's speech usage should somehow reveal, even though somewhat remotely and indirectly, some implications of the development of one's interpersonal attitudes.

The speech of schizophrenic patients has long attracted attention because of the curious nature of its distortion of normal linguistic usage. It is not that the schizophrenic patient invariably uses words peculiar to himself, though sometimes he does. It is not that he uses words invariably with unfamiliar meanings, though sometimes he does. It is rather the total effect of schizophrenic speech that is striking. This may vary from stilted and formal phraseology without apparent substance to a "word salad" of nouns and verbs with practically no articulated structure, or even without apparent meaningful connection.

In the present paper we submit the results of a quantitative investigation of the frequency and diversity of the words used in a series of intimate letters written by a young woman, Helen B., while institutionalized for paranoid schizophrenia. To these quantitative data we shall add a bit of interpretation, in the belief that we may be able thereby to shed some light on the dynamics of this disorder, in which meanings seem at times to go far astray. The material chosen for this study is not the grossly disordered type of speech called "word salad" but personal letters, in which the language does not seem on casual inspection to deviate notably from

From the Department of Psychiatry and the Henry Phipps Psychiatric Clinic, Johns Hopkins University and Hospital, and Harvard University.

The clinical material was from the experience of Dr. Whitehorn, at McLean Hospital. The statistical analysis was conducted under the direction of Dr. Zipf.

This work has been aided in part by a grant to one of us (Dr. Whitehorn) from the Masonic Fund, administered by the National Committee for Mental Hygiene. The preparation of the manuscript and charts was subvented by a grant to the other (Dr. Zipf) from the Committee on Research in the Social Sciences, Harvard University.

normal language customs. In order to place our data for schizophrenic language in a suitable perspective against the background of nonschizophrenic language, we also studied some control material. We shall begin our presentation by briefly discussing certain characteristics of the language of normal adults.

REPETITIOUSNESS VERSUS DIVERSIFICATION; ANALOGY OF TOOLS

The method of statistical study here employed is one which may appear somewhat stilted and oblique, since it intentionally avoids any direct effort to deal with the speech productions as immediate expressions of meaning. We do not intend to imply that the content of speech—what one means to say—is of no consequence, but we are reporting here on interesting characteristics of form, ignoring content. We shall begin with a consideration of normal discourse. A certain relation has been found empirically between the number and the frequency of use of different words in various samples of discourse. We wish to present our observations quite objectively, but it may be helpful, also, to have in mind a tentative working hypothesis. We shall assume, in the company of many others, that speech is a socioeconomic device for saving effort in the attainment of objectives.¹ With this explicit assumption in mind, one may ask how an urge to economize in effort might affect the size or diversity of a person's vocabulary, as well as the frequency with which he uses his words.

Obviously, there might be an economy of effort in having a vocabulary that consisted exclusively of only a single word which could be used for all verbal purposes. The single word would save the speaker the "mental effort" which would be necessary in order to "think of" the "right" word if he had a large vocabulary of different words to choose from. We may tentatively visualize a tendency constantly operating in the direction of reducing the number of different words in a vocabulary toward the limit of one single word which would have a frequency of 100 per cent and which would mean everything. We shall henceforth designate this as the tendency to repetitiousness, since it tends to compress all meanings and all diversity of vocabulary within a few words, often repeated.

Opposed to this tendency to repetitiousness is the economy that is available in a vocabulary that possesses a distinctly different word for each different meaning to be verbalized. This second economy would work to make discourse easier for the auditor, if he knew the vocabulary, since it would save him the mental effort that would otherwise be necessary to excogitate, or determine, the particular meaning to which a given word refers. Such an advantage to the auditor would in normal speech, for practical purposes, be an advantage to the speaker also. We may visualize this tendency as one that would constantly operate in the direction of increasing the number of different words in a person's vocabulary until there would be m number of different words, with one each for the m number of different meanings to be verbalized. Since the net effect of this tendency would be to increase the verbal diversity of a person's vocabulary, we shall henceforth call it the tendency to diversification.^{1b}

Now, every speech production would apparently be subject to these two opposing tendencies: the one tendency (repetitiousness) making for a vocabulary of one word, with m meanings, and the other (diversification) making for a vocabulary of m words, with one meaning each. Every actual speech production, subject to these opposing tendencies, would tend toward an intermediate condition, in which

1. (a) Zipf, G. K.: *The Psycho-Biology of Language*, ed. 2, Boston, Houghton Mifflin Company, 1939. (b) For a discussion of the philosophic basis of the postulate of least effort (least action), see Zipf, G. K.: *The Unity of Nature, Least-Action, and Natural Social Science, Sociometry* 5:48-62, 1942, and footnote 7.

there would be fewer than m different words and in which no word would be used exclusively. It is obvious that actual speech does represent an intermediate condition between the extremes of these tendencies, but what is not nearly so obvious is the fact that actual samples of language behavior do show an extraordinarily steady equilibrium between these tendencies.

In speaking of an equilibrium in speech between the described economical tendencies to repetitiousness and to diversification, we imply by no means that speech is therein unique. An artisan's set of tools is also subject to the same forces of economy.² Thus, there is an economy in 'possessing a single tool that can be used for the performance of every task (repetitiousness). Conversely, there is an economy in possessing a specialized tool that is designed for the economical discharge of each different task (diversification). And, doubtless, in the evolution of tool design these opposing tendencies to repetitiousness and diversification have been operative in producing, on the one hand, single tools of general use and, on the other, different tools of specialized use.

We mention the case of a set of mechanical tools not merely to remind the reader of the prevalent belief that "words are tools," but to suggest that fundamentally the forces which may motivate the number and uses of different tools are the same as those which may motivate the number and uses of different words. We shall return subsequently to a reconsideration of this word-tool analogy.

STATISTICAL BALANCE IN ADULT LANGUAGE

A rather remarkable type of equilibrium in respect to the diversity and frequency of use of words can be shown by an appropriate statistical analysis of the number of different words and their frequency of use in actual samples of running speech.

In figure 1 we present the statistical analyses of two sizable samples of speech. The one curve (*I*) is for the 29,899 different words in fully inflected form as they appear in the total of 260,430 running words in James Joyce's novel "Ulysses," as determined by Hanley.³ The other (*II*) represents Eldridge's analysis⁴ of the 6,002 different words in fully inflected form as they appear in a total of 43,989 running words in combined samples of American newspapers.

In the construction of each of the aforementioned curves, as well as of all others presented in this paper, the statistical data were arranged and displayed on the charts in the following fashion: First, every occurrence of every word in a given sample having been noted (each inflected form being counted as a distinct word), the words were arranged in rank in the order of frequency. The most frequent word in a given sample—in English it is generally "the"—has the rank 1. The next most frequent word is usually "of"; yet whatever the word may be, it has the rank 2. The third most frequent word, whatever it may be, has the rank 3, and so on. The least frequent words are of course those which occur only once in the sample, and of these there will be a considerable number, all occupying the terminal ranks. It will also happen regularly in the intermediate ranks that a number of different words will be found occurring with equal frequency in a given sample, and they are assigned the ranks between the group of words just higher and those just lower in frequency. The terminal rank (i. e. the rank of the last word) will

2. Zipf, G. K.: On the Economical Arrangement of Tools, *Psychol. Rec.* 4:147-159, 1940; *National Unity and Disunity*, Bloomington, Ind., Principia Press, 1941, chap. 3.

3. Hanley, M. L.: *Word Index to James Joyce's Ulysses*, Madison, Wis., University of Wisconsin Press, 1937.

4. Eldridge, R. C.: *Six Thousand Common English Words*, Buffalo, N. Y., The Clement Press, 1911. (A copy of this treatise is in the Library of Congress.)

obviously represent numerically the total vocabulary of different words in the sample. To display the results in graphic form, these ranks are plotted successively from left to right along the abscissa, and the corresponding frequency for each rank is indicated by a dot at the appropriate height on the ordinate. If there is only one word having a certain frequency, it gets a dot; a group of words of equal frequencies get a horizontal series of dots. If the ranks are plotted on ordinary arithmetical coordinate paper, a sweeping curve is formed closely hugging the axes, something like the familiar pressure-volume diagram of Boyle's law when it is plotted over a wide range. When plotting is done on doubly logarithmic coordinates, as here, the successive dots fall on a curve closely approximating a straight line (for the sake of greater clarity, we have connected the successive dots with lines). The decrease in frequency at each step, in passing from left to right

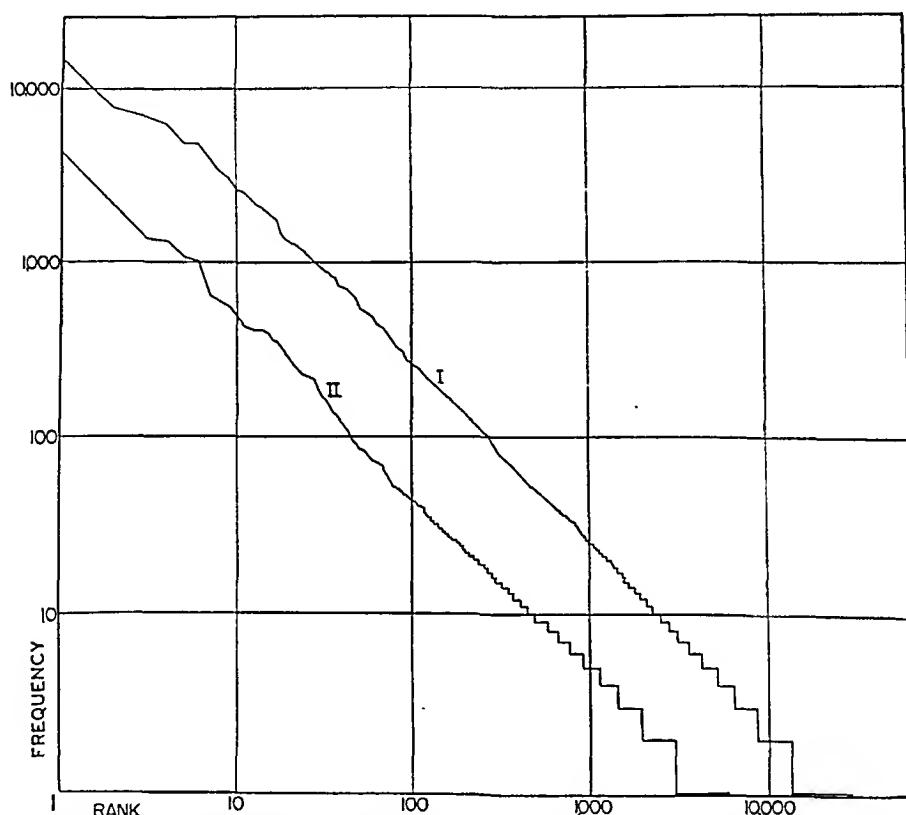


Fig. 1.—The rank-frequency distributions of words in (I) Joyce's "Ulysses" and (II) American newspapers (Eldridge analysis).

in accordance with the rank of the words, is inevitably from the definition of rank. The point of mathematical significance lies in the fact that the successive steps have just the right magnitude at each step to approximate a straight line.⁵ In

5. To our knowledge, the first person to recognize as such the hyperbolic nature of the frequency of word use was the French stenographer J. B. Estoup (*Gammes sténographiques*, ed. 4, Paris, Bureau du l'Institut Sténographique, 1916). (We have not seen the first edition, which appeared in 1907.) Others subsequently observed the same general relationship in various languages, without attempts at precise formulation. The first precise formulation in terms of a negative slope of 1 was by E. V. Condon (*Statistics of Vocabulary*, *Science* 67:300, 1928). The formulation in terms of a harmonic series was first made by J. C. Whitehorn and presented anonymously by Zipf,¹¹ p. 44. For a mathematical treatment of the magnitudes of the successive steps and the equation $R \times F = C$, see Zipf, G. K.: *Homogeneity and Heterogeneity in Language*, *Psychol. Rec.* 2:347-367, 1938.

algebraic terms, the rank (R) of a word, when multiplied by its frequency (F), yields a constant (C). This is the familiar equation of an equilateral hyperbola, $R \times F = C$.

This equation may be made somewhat more readily "understandable" by reference to our previously discussed tendencies to repetitiousness and diversification. Since diversification acts in the general direction of increasing the number of different words, and hence the size of the final R , and since repetitiousness acts in the general direction of increasing the frequency of their use, and hence the size of F , we may interpret this equation to mean that the tendencies to repetitiousness and diversification stand in an inversely proportional relationship to one another—that is, in the dynamic relationship of an equilateral hyperbola.

Many samples of speech have been analyzed in this fashion. The relationship $R \times F = C$ is found to be a general first approximation to the truth, and so serves as a convenient base line for the disclosing and analyzing of deviations.

THE SPEECH OF CHILDREN

We have previously assumed that the limit of the tendency to diversification would be a vocabulary of m different words which would match in 1:1 correspondence the presumed m different meanings to be verbalized by the speaker in a given sample of discourse. As to the number of different meanings, m , in that sample we have made no assumption. According to our argument, whatever the size of m may be, the size of n (the actual number of different words) will be smaller than m .

Once we broach the question of the size of n , we are reminded of the vocabularies of children empiric analysis of which has long shown that the vocabulary used is on the whole comparatively much smaller than the average adult vocabulary. Since the speech of psychotic persons is sometimes likened to the speech of children, the present momentary digression on the diversification and frequency of use of children's words may serve a useful purpose, not only in establishing some objective criteria for children's speech but in deepening insight into the general nature of disordered speech.

In investigating by this special statistical technic the limited diversity of a child's word vocabulary, we first ask whether a small n for the words of a child's vocabulary, as revealed in a sample of speech, is matched by a correspondingly low frequency of use, with the result that the child's rank-frequency distribution of words is faithfully described by the hyperbolic equation $R \times F = C$. Such a hyperbolic relationship does, in fact, seem to exist, according to the results of a quantitative investigation completed by one of us (G. K. Z.) and reported in preliminary form elsewhere.⁶ The upshot of this investigation of children's speech, which will be presented in detail in a future publication,⁷ is that the rank-frequency distributions of children do indeed follow fairly closely the hyperbolic equation. In this connection we submit in figure 2 (*I*) the rank-frequency distribution of a 10,000 word sample of a 5 year old girl's speech, as recorded by Uhrbrock,⁸ and (*II*)

6. Zipf, G. K.: *Children's Speech*, Science **96**:344, 1942.

7. Zipf, G. K.: *The Principle of Least Effort*, to be published. Children's speech material will be reported in full in chapter III of this book.

8. These are the recordings discussed by R. S. Uhrbrock: (*Educ. Research Bull.* **14**:85-97, 1935; *J. Educ. Psychol.* **27**:155-158, 1936). Dr. Uhrbrock put at the disposal of one of us (G. K. Z.) a transcript of the recordings.

that of a 4,000 word sample for the same child at the age of 6 years.⁹ It is evident from the two curves in figure 2 that they are approximating essentially the same slope of the hyperbolic equation observed for adult speech in figure 1.

The child's curves in figure 2 show, however, a more marked deviation from a straight line than do the more mature samples in figure 1. One may say that the curves bulge upward in the middle region, the 5 year curve bulging most at about rank 30 and the 6 year curve bulging most at about rank 50, but to a noticeably less degree. Or, alternatively, one could say that the words in the upper several ranks and in the lower several hundred ranks are used less frequently than would be proportionate to the use of the words in the middle ranks, as judged by deviation from the equation of an equilateral hyperbola.

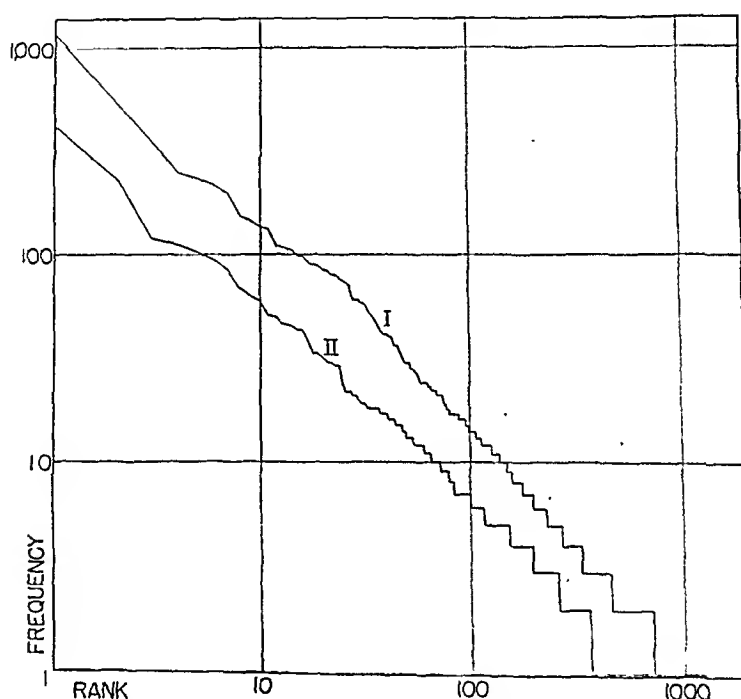


Fig. 2.—The rank-frequency distributions of (I) 10,000 running words of a 5 year old girl and (II) 4,000 running words of the same girl at 6 years of age.

CHILDISH VERBALIZATION OF ADULTS

A case of special interest for the "childish" type of discourse is provided by our study of a patient, Miss Margaret C., who was a highly trained and fairly productive scientist, but childish in the character and expression of her emotional relationships. After a brief account of her clinical picture, we shall present the rank-frequency distributions of the words of her intimate personal letters, and we shall note the extent to which her speech is graphically like that of a child.

Miss Margaret C.,¹⁰ a 33 year old chemist from the University of W., while on a brief visit with relatives in Boston, announced that she had just gotten into telepathic communication with two close friends and thereby learned that one of them (a man of 40) wished to marry her and that the other (a woman of 50) had just become a mother (*her* mother). Brought

9. From a transcript of recordings made by R. S. Uhrbrock and put at the disposal of one of us (G. K. Z.) by Dr. Uhrbrock.

10. The names of patients are fictitious, and to preserve their incognito certain relatively insignificant facts have been disguised.

to McLean Hospital, Margaret seemed at first in high spirits and spent many hours observing in herself the sensations of a newborn baby, when, for example, she was in a wet pack. She promptly decided that the proposal of marriage had been an error, but it took about three weeks, and an interview with the friend in question, for her to decide that she had not been reborn to the new mother. By this time she asked one of the hospital physicians to be like a father to her. She found obvious difficulties in keeping frankly erotic impulses out of this relationship and passed into a catatonic condition, standing rigidly for hours, with saliva drooling. In moments of excitement she spoke of herself as the "Christ child" and repeated verbatim "messages" from Jesus Christ, from old friends and from others who were dead, and she gave many evidences of being in hallucinatory contact with her father, whom she had really never known, as he had died when she was an infant. After a stormy illness of about three months, she rather suddenly improved and, on her insistent request, was discharged to return to her research work at the University of W. Her psychosis could be characterized as "schizoaffective."

Margaret was the youngest of two children, brought up fatherless by a hard-working mother, not very affectionate, who succeeded in providing excellent college and professional educations for her two children. Margaret was intellectually brilliant and was making a distinguished career in research, but had a characteristic difficulty in personal relationships. She attached herself to older women with inordinate devotion and suffered proportionate distress when they grew restive and drifted out of these relationships. At the time of the onset of her psychotic episode, Margaret had just suffered the termination of the most recent of such attachments, which had been in some respects the most gratifying, for this woman had cooperated for a time in a "make-believe" correspondence, in which Margaret had addressed her as "dear Granny," in fond memory of her paternal grandmother, who had provided Margaret's happiest childhood experiences.

After her discharge from the hospital Margaret wrote frequent letters to her favorite physician (the one whom she had adopted as a father in her illness) and asked permission to address him as "dear Daddy" in her letters. On this basis a kind of long distance supportive psychotherapy was carried on for six or seven years, which was aimed ultimately at helping her outgrow somewhat her childish personal dependence. Margaret continued in her research work, which has now gained her considerable scientific distinction, including an honorary Sc.D. The long distance therapy had its awkward features, and the process of "weaning" precipitated three episodic recurrences, for a few days each, of the kind of psychotic reaction shown on the first hospitalization, but Margaret has now been doing well, practically without the physician's letters, for four years. Her letters constitute the material of the present study. A few quotations indicate their general style and substance:

Aug. 12, 1931: "The laboratory work was misery for the first few weeks. If I could have done some quantitative work I should have been all right, but I had to finish writing my paper for the J. P. C. and the sentences were stubborn and didn't seem to want to be written, and I was blue and hot and tangled up in mathematics and the theoretical part of the paper, and wanted nothing so much as to go to sleep all the time . . . I had my friend Dorothy convulsed with laughter the other day when I told her how I suffered at the hospital from making people dress me when I would much rather have dressed myself, and drew for her a graphic picture of the hearty and mutual dislike between Miss M. and myself as we went through these ordeals. She laughed till she nearly cried while I pictured for her Miss M. feeding me with a spoon and me squirming under it!"

March 12, 1932: "Dear Daddy: I've just been having a fit of temper about the way A— has treated me. I guess maybe I'm ashamed of myself to behave like such a baby. And you will feel ashamed of me and that will make me feel badly. And maybe that will make me stop."

Dec. 26, 1934: "O Daddy, it's so nice to be alive—I mean really truly living. It's as if I'd never really lived before I was in the hospital—I had always been stewing about something or other all my life—even since I can remember I used to stew about things. And now I don't care any more."

In figure 3 we present rank-frequency distribution for the whole and for parts of 50,000 running words of the intimate personal letters of Margaret. Curve *I* represents the total 50,000 running words, and curve *II*, the last 30,000 words; curves *III* and *IV* represent the first and second blocks of 20,000 words each (i. e., 1 through 20,000 and 20,001 through 40,000); curve *V* represents the first 10,000 running words; curves *VI* and *VII* represent the first and second blocks of 5,000 each (i. e., 1 through 5,000 and 5,001 through 10,000), and curves *VIII* and *IX*,

the first and third blocks of 2,000 running words each. Lines *A* and *B*, which have been added for comparative purposes, represent the ideal slope of an equilateral hyperbola.

The nine curves of figure 3 reveal several types of bends. Of no significance for this study—and we shall discuss this point at the outset in order to dismiss it from further consideration here—is the striking bend at the top of the curves with the concave side downward, which represents roughly the 10 most frequent words (i. e., ranks 1 to 10) and which has a slope that is much less than that of *A* or *B*. This particular bend, which for convenience we shall henceforth term the top concavity, represents nothing more than the fact that the words were taken from letters that were intimately personal, and not formal; in and for itself the top concavity has no necessary connection with abnormality. Indeed, as early as 1936

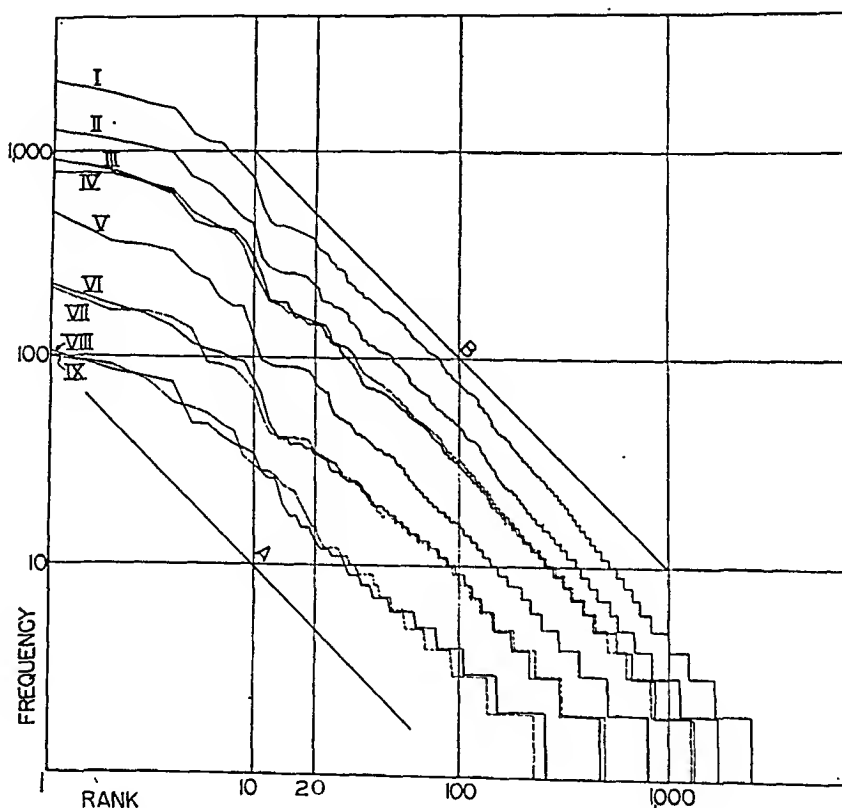


Fig. 3.—Rank-frequency distributions for Margaret C. (a “childish” adult) in samples of (I) 50,000 words; (II) 30,000 words; (III and IV) 20,000 words; (V) 10,000 words; (VI and VII) 5,000 words, and (VIII and IX) 2,000 words.

In this figure, and in figures 4 and 5, *A* and *B* are ideal standard curves.

one of us (J. C. W.) observed the presence of a top concavity rather generally also in the word frequency analysis of the intimate letters of normal persons. Subsequently, the other of us (G. K. Z.) assigned the topic of top concavity for further investigation to three of his students, W. A. Burnham Jr., H. Shippen Goodhue and Kermit Roosevelt Jr., who carefully analyzed the frequency distributions of words in extensive sets of intimately personal letters and found in all cases a top concavity. In this connection we suggest that the presence of a top concavity in intimately personal (i. e., not formal) letters may be ascribed to the fact that the writer and the reader have a certain commonness of experience and hence can dispense with the high degree of articulation that is otherwise necessary in writing to a nonintimate. Thus, to the close friend or relative one may simply refer to

Mary, John and Ned, without explaining that one is the cat, the other the chauffeur and the third the dog. In brief, the definite articles and other short, highly frequent articulatory words, which are necessary for coherence when one is writing to a person who is a stranger to the topic, become unnecessary in writing to the intimate. It is the substandard frequency of these articulatory words which is found in colloquial and intimate writing (and speaking) and which is reflected in a top concavity.¹¹ Presumably, also, the slight top concavity in "Ulysses" (curve *I*, fig. 1) has a similar explanation.¹²

When one turns to a consideration of the middle and lower portions of these curves, and inspects first the largest samples in the figure, one notes that the curves have still a general concave appearance, comparable to the 5 year old child's curve in figure 2, with the bulge, or bend, at about the point of ranks 50 to 100. Above this point the slope is slightly less than that of *A* or *B*, whereas below this point the slope is slightly greater.

This bend, which may be connected with "childishness," can perhaps best be understood if one notes that it is absent in the 2,000 word samples of curves *VIII* and *IX*. Indeed, since these 2,000 word curves, except for a top concavity, approximate fairly closely the hyperbolic equation, $R \times F = C$, it follows that Margaret's speech is balanced with about 500 different words in a discourse of about 2,000 running words. Of course, Margaret's vocabulary contains more than 500 different words, as can be seen in curve *I*, in which the final rank is approximately 5,000. But the point is that Margaret favors the limited vocabulary of 500 odd words, as the bends in the larger samples show, and she favors them at the expense of the rarer conceptual words. This favoritism becomes ever more conspicuous as the size of the sample is increased.

Stated in terms of the tool analogy, this bend perhaps means that Margaret lives in a workshop with a respectable number of different verbal tools (i. e., about 5,000), which are designed for specific verbal tasks. Though she knows the uses to which these different tools can be put, for she does not avoid them altogether, nevertheless she prefers the simpler tools to the more specific ones. Hence she uses her verbal tools in a manner similar to that of the child, even though she may possess the verbal equipment of the adult. Thus the bend in her rank-frequency distributions of words may be construed as being ultimately connected with the observable "childishness" of her behavior. In short, our linguistic data may be indicative of a condition of mind of far greater extent than that of the merely verbal field.

Before leaving figure 3, we call attention to the bend with the convexity downward which occurs systematically in the neighborhood of rank 12 (i. e., from ranks 11 to 13) in curves *I* to *VII* and is lacking in curves *VIII* and *IX*. Since this bend is present in all the larger samples, and since it is of the same kind and is located in the same position in the upper curves, i. e., it is systematic, we may not ascribe its emergence to chance. Though limitations of space prevent a more detailed analysis here, we may, nevertheless, remark that a bend of this type may represent a disunity, or lack of homogeneity, of discourse.¹³ That is, Margaret in

11. For discussion of articulatory and conceptual words, see Zipf,^{1a} p. 229.

12. One of us (J. C. W.) has noted an interesting, and perhaps significant, exception to this very general rule in the published correspondence of George Bernard Shaw and Ellen Terry (New York, G. P. Putnam's Sons, 1932). The language of the former shows a relative excess of articulatory terms (as if he were composing his letters for a number of readers), whereas the actress' language is normal in this respect.

13. Zipf, G. K.: Homogeneity and Heterogeneity in Language, *Psychol. Rec.* 2:347-367, 1938.

her workshop does not simply use a limited number of tools, like a child, in obtaining her day to day objective. She apparently has a limited number of fixed jobs, which are not integrated in her total scheme of living and on which she apparently persists in working with a limited number of tools.

The gross statistical meaning of the curves of figure 3, aside from the top concavity, which we expect to find in intimate personal letters, is that they represent the distributions of an unbalanced person. This lack of balance is the kind one might expect of a child in an adult's workshop. The language is not only "childish"; it lacks integration.

PARANOID LANGUAGE

Another large sample of control material became available when one of us (J. C. W.) found a large collection of letters written by Charles M., who was a patient at McLean Hospital in the years before the Civil War. The letters themselves constitute the main source of information about him. In terms of present day psychiatric characterization, his illness would be described as a paranoid condition, with a rather pronounced manic tendency, not only for letter writing but for traveling and making friends. It is doubtful whether one could correctly call him schizophrenic in the same sense that one does Helen B., whose case is to be described later, but he comes very near it. There are evidences of hypochondriacal tendencies; for example, he was apprehensive about "drafts" blowing on him. At least on one occasion he wore two suits of underwear in September, and at another time, while in the asylum at Columbia, S. C., he wrote about having to wear two overcoats to keep warm. Indeed, some of his paranoid suspicions of his father and certain friends and physicians were developed around the theme of their alleged attempts to kill him by making him catch a severe cold. In this connection, it is of interest that his first major psychiatric difficulty involved a "draft" on a bank, apparently forged in New York, when he was financially embarrassed while returning to his home in Charleston, S. C., after a trip to Niagara Falls with a chance acquaintance, who proved to be a gambler. His most bitter paranoid accusations centered around delusions of food poisoning. He suspected that "sugar of lead" was put in his food and drink and dusted into his room. As an illustration of his friendly disposition, it is noteworthy that in making an escape from the South Carolina institution, he planned it in a way to exonerate from blame the attendant who was accompanying him on a buggy ride. Yet, for the most part, he included in his paranoid suspicions most of the friends who tried to help him.

M. was an unmarried man of good family and high social position in South Carolina and had had his college education at Harvard and in Paris. His first commitment as insane occurred in 1852, at the age of 29, in Columbia, S. C., after quarrels with his father over his demands for a large share of the family estate. At this time he became suspicious of all in the family, sat up most of the night with a poker in his hand for protection and apparently had auditory hallucinations and ideas of reference. After about four months he escaped to "the West." In Tennessee he seems to have impressed friends as normal but showed in letters obvious paranoid attitudes. He was at home for some months in Charleston in 1853. In 1854 he visited Cuba and Europe and also made a trip to Boston to attend a reunion of his college class. But on September 20, a few days before the reunion, he was hospitalized at McLean Asylum, where he remained for some years, obviously touchy, cantankerous and paranoid, but apparently without hallucinations. He remained hospitalized until his death in the 1870's.

Characteristic quotations from his letters are given here.

In 1852, to a lawyer, whom he asked to undertake his case against his father: "I enclose a narrative of what occurred at the Insane Asylum at Columbia during my confinement there in the winter of 1852-53, and five letters which will throw a great deal of light on the causes that led to that confinement. . . .

"The letter of Pinkney H. is a tissue of falsehood and hypocrisy, and I think the fact that he did not attend to my rights of liberty is sufficient evidence that he could not have referred to them when he said that he would see that I had my rights, and renders probable the charges that I intend to bring against Russel M. and himself, namely, that their services were given to my father as the price of my blood. . . .

" . . . My object in enclosing the Narrative is that you will read them with the view to a question of property between my father and myself. My narrative is in every respect a faithful one. If it were not, it could not escape the practiced scrutiny of a great lawyer, and while it awakens your deep indignation at the harsh and unfatherly act which consigned me with such cold-blooded barbarity to the abhorred and forgotten end of a lunatic, I hope it will indicate with sufficient clearness the true cause that led to his course, which was the necessity for maintaining himself in the possession of property to which I had a legal

claim by the will of Francis K., and of which he therefore held fraudulent possession. The evidence on this point is, I think, very conclusive, and my intention is that my rights shall be tested by an appeal to law. If your conviction is the same, and you are willing to act for me as my lawyer I will pay you in case of a favorable decision twenty thousand dollars . . .

"I shall be able to raise enough money to carry on the suit, on your opinion as to the justice of my claim, and an arrangement for your own security while in Charleston can readily be made with any of the hotel keepers. . . .

"There is another circumstance to which I will allude. The moment that I heard of the death of Mrs. B., I comprehended the true cause of it, but while I was in Nashville I did not think that her relations had suspected that dark, and infamous act, and when Mrs. F. showed me the paragraph in which it was suggested that the sun was the origin of the gulf stream, I did not suppose that she knew that I was the cause of her sister's untimely end. I regret that I should have been the cause of the death of an amiable and accomplished woman, in whose society her friends delighted, but one of her murderers, Dr. B., is I think in my power, and I shall make him atone for his crime by convicting him, if I can, of perjury."

In 1853, to the friend Pinkney H., named in the foregoing letter: "I desire to make a few remarks on a letter that I received from you not very long since. I have already convicted you of one falsehood. It is now my intention to convict you of something worse than a falsehood—to convict you of having deliberately made me a promise, and of having just as deliberately broken it. I refer to your promise that 'you would see that I had my rights.' This assertion you say had reference to my rights of liberty. What steps were taken by you to have my rights attended to? Did you ever return to Columbia to inquire how my health was progressing? Did you see that the promise, made by my father through Dr. B. in your presence, and for which you were responsible, that I should remain at the Asylum only two or three weeks, was carried out in good faith? Instead of remaining at the Asylum only two or three weeks, I remained there nearly four months, being subjected incessantly to every mode of torture by poisons, and during the whole of that time neither you nor any of my other relations came to see me. You had abandoned me to the horrors of a future lost on earth. How then was your promise redeemed? It is needless to disguise the truth. Your promise, whether it had reference to property or to liberty, was not made in good faith . . ."

In 1859, a long, and rather formal, document begins as follows: "The History of a Lunatic, written for the Honorable Edward Everett, for he was Secretary of State for the United States of America in December 1852, when my insanity was discovered. A graduate of Harvard College. Addressed to the Congress of the United States, and the Legislature of Massachusetts. By Charles M. . . .

"It is the public law of each State that a person suspected of derangement shall be confined in a Lunatic Asylum on a warrant issued by a magistrate placing his person in custody of a physician connected with such an institution. I am a resident of South Carolina and a warrant was issued by a magistrate in Charleston placing me in custody of Dr. J. W. Parker of the Insane Asylum at Columbia. I remained at Columbia three months and a half, from December 5th, 1852, until March 24th, 1853. I then made my escape and went to Nashville in Tennessee which I reached after three weeks hard riding on horseback. . . .

". . . I graduated at Harvard College in 1844, but I am not an accomplished man. I prefer being an audience to the United States rather than one of her legislators. I am not contaminated, nor do I intend to be. I always held the opinion that the human mind could resolve all doubts with reference to its existence, and I have always cordially supported the Republic, and countenanced fanatics, and extremeists. My father holds moderate public opinions, but very harsh, severe and despotic private opinions. He claims that a father has absolute control over his children. That he may put them to death or sell them, another law of South Carolina publicly supports him in this. He does not believe that a tyrant is degraded in his own estimation by despotic acts, and therefore no one is his equal. In the management of his children (the eldest is thirty nine and the youngest nineteen) he allows no advice from his wife. . . .

"The Asylum occupies one of the squares in the Town, now the city of Columbia. The building is composed of a square center, and two wings of equal length. It has two yards attached, one in front of the Asylum, out as a garden with iron railings and iron gates, the other has high walls and is divided into two lots where the male and female patients, or mad men and women exercise. The Asylum has become very wealthy of late years, from large sums of money having been paid to the Regents or Trustees to get rid of certain insane heirs (this is not a legal conclusion but my own conjecture.) and since 1853 they have had another square erected to the buildings which they have surrounded by a high wall. The inmates who are placed here are as absolutely certain of being killed or cured, as it is absolutely certain that

John Brown was hung. These Asylums everywhere in the United States are taking the place in the respect and even the idolatry of men that convent and monasteries occupied in England. They are very wealthy, very despotic, and do not represent. . . .

"... I supposed for some time that the Asylum was constructed in such a way that the sounds could be carried to one room, and then listened to when the physicians or attendants wished to know what the patients were about, but I am of opinion now that no such whispering tubes existed. . . ."

In figure 4 we present the rank frequency distributions of words in the whole and in parts of Charles's letters and extensive autobiographic material contained therein, which totaled 47,850 running words and hence fell slightly short of the arbitrarily selected 50,000 running words represented in figures 3 and 4. Here curve *I* represents 47,850 running words; curve *II*, a block of the last 27,850 words (i. e., 20,001 through 47,850); curve *III*, the first 20,000 (actually 20,005) words;

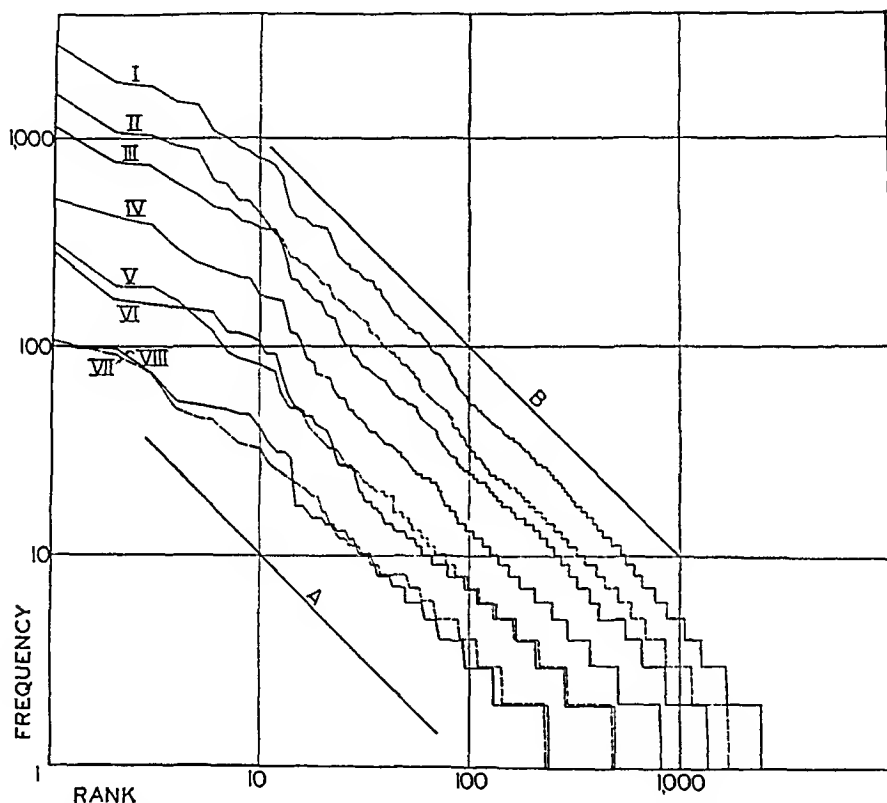


Fig. 4.—Rank-frequency distributions for Charles M. (a paranoid patient) in samples of (*I*) 47,850 words; (*II*) 27,850 words; (*III*) 20,000 words; (*IV*) 10,000 words; (*V* and *VI*) 5,000 words, and (*VII* and *VIII*) 2,000 words.

curve *IV*, the first 10,000 words; curve *V*, the first 5,000 words; curve *VI*, the second 5,000 words; and curves *VII* and *VIII*, the first and third blocks of 2,000 words each. Lines *A* and *B* have been added, as previously, in order to aid the reader's eye.

If the reader sights down the eight lines from the top and ignores the top-concavity as well as the slight differences in general slope,¹⁴ he will note that the curves do not have the general concave appearance of Margaret's, but that

14. The slope of the line of a rank-frequency distribution will depend, among other things, on the size of the sample. For an ingenious mathematical discussion, see Carroll, J. B.: Diversity of Vocabulary and the Harmonic Series Law of Word-Frequency Distribution, *Psychol. Rec.* 2:379-386, 1938. Carroll's study will be found criticized and the topic further explored by one of us (G. K. Z.) in his forthcoming book.⁷

curve *I* bends slightly at about rank 300. This may constitute some slight evidence of what we previously described as "childishness," but with the curve displaced some 200 ranks to the right. This slight bend is also present in curve *II*, and perhaps in curve *III*. It is not apparent in curves *IV* to *VIII*. Hence up to this point Charles's vocabulary is fairly normal.

Nevertheless, these eight lines have one other characteristic—their general waviness, which on the whole is not systematic, in the sense that the same type of bend is not found with reference to the same ranks, as was the case to a considerable extent with Margaret's. Indeed, in comparison with the irregular waviness of Charles's curves, Margaret's parallel each other fairly consistently throughout, and hence point to a systematization¹⁵ that is lacking in Charles's curves.

The unsystematic waviness of Charles's curves of word distribution may conceivably indicate that his stream of speech was not confined to systematic grooves. Whether one may actually read anything pathologic into this random waviness is doubtful. In terms of our tool analogy, Charles was apparently using a large diversity of tools in a reasonably close balance between the tendency to repetitiousness and the tendency to diversification. He may merely have concentrated excessively now on one group of tools and now on another or others, with the result of a certain waviness.

AUTISM OF PARANOID SCHIZOPHRENIA

Up to this point we have presented rank frequency distributions for the words of professional adult writers (fig. 1), for a child (fig. 2), for a "childish" adult (fig. 3) and for a paranoid patient (fig. 4). Though these language productions differed in some respects, they could all be referred ultimately to the fundamental hyperbolic equation, with its assumed balance between repetitiousness and diversification, and their differences were most conveniently displayed by graphic comparison with this equation. Moreover, in all the foregoing cases the analogy of mechanical tools in a workshop seemed on the whole legitimate.

But now that we turn to a consideration of the verbalizations of the patient with paranoid schizophrenia, Helen B., we come on a curious and systematic distortion of a type not present in the preceding material.

In order to prepare for an inspection of her word distributions, we may for a moment probe more deeply into the economies of the tendencies to repetitiousness and diversification for the light that they may shed on the speaker's attitude toward the author (or the writer's attitude toward the reader). It is remembered that the economy of the tendency to repetitiousness, which strives to subsume m different meanings under one single word, is an economy that works to the convenience of the speaker. On the other hand, the tendency to diversification, which strives to increase the size of a vocabulary to m different words, with one meaning per word, is based on an economy that works to the convenience of the auditor. Therefore, the balance between the tendency to repetitiousness and the tendency to diversification would seem to refer also to a corresponding balance between the respective conveniences of the speaker and of the auditor, with the ultimate result that the y coordinate (frequency) will represent the "pull" of the speaker's convenience, whereas the x coordinate (diversity, in terms of rank) will represent the "pull" of the auditor's convenience, the assessment being made by the speaker in both cases. In other words, the hyperbolic equation, $R \times F = C$, may be equivalent to $U \times I = C$, in which U represents the speaker's consideration for

15. Whitehorn, J. C.: Material of Human Nature and Conduct, *Am. J. Psychiat.* **92**:315-323, 1935.

"the other fellow," as measured on the horizontal axis, and I represents the speaker's consideration for himself, as measured on the vertical axis. As long as the distribution is truly hyperbolic, one may imagine that these "egocentric" and "allocentric" forces are balanced without bias to either.

But suppose that the distribution favors repetitiousness (or I), at the expense of diversification (or U)—what then? In this case the speaker may be considering his own convenience more highly than that of the auditor. We shall designate this egocentric condition as autistic. By autistic, however, we do not mean all egocentricity in whatever form it may appear in speech. An egocentric person who wishes to dominate his environment is not necessarily impelled to be autistic in this sense and to sacrifice the auditor's speech convenience to his own. On the contrary, an unscrupulous politician or a confidence man can accomplish his egocentric goals within the normal use of speech, and with normal, or even super-normal, considerateness for the convenience of his auditor. The dictator, in hounding his minions, gains nothing by issuing decrees in a verbiage which the minions will find difficult to understand. Rather does the dictator use language that is unambiguous to his auditor. A given person may, and often enough does, use language to gain his own personal ends against another person; in so doing he will commonly find it to his own advantage to defer to the other's verbal convenience. By autism, then, we do not mean the egocentric attitude of exploiting others, but rather the egocentric tendency to disregard the convenience of others.

Such an autistic tendency might distort a rank-frequency distribution of words by crowding an inconveniently large number of meanings onto a relatively small number of words. Conceivably, it might also happen that a person, inconsiderate of others, might indulge in a diversified polysyllabic discourse, using such a large and unfamiliar vocabulary as to be incomprehensible to most.

We shall now consider the actual observations on a selected patient.

Miss Helen B., a 23 year old, unmarried college student, was admitted to McLean Hospital in 1931 because of screaming denunciations against father, mother and sister for their "insidious actions," accompanied by threats to kill them. This incident came as the climax to two years of psychotic maladjustment at home, which had started as an episode of tearful panic while she was in her third year at college. That episode had been preceded for a year or more by mounting tension within the family and quarrels with and about "lovers."

At the hospital the screaming mood subsided within a few minutes, and the patient settled herself fairly comfortably in her quarters. With little questioning she expounded volubly the "plot" which menaced her. In brief, she stated that there was a conspiracy by the closed ring to make a prostitute of her. The conspiracy, she said, included her father, her various lovers, the Secretary of the United States Treasury, the Pope, the whole Roman Catholic Church, the Masons, the Methodists and a long list of other persons. The closed ring, she said, had also recently instigated an invasion from Mexico, to prevent which President Hoover had put battleships on the coast of California. She "feared" that the government would be overthrown by the closed ring and that she would be killed when they got in power. Within a few days she included hospital personnel in the "conspiracy" and spoke of being spied on by television and radio apparatus in the ventilator of her room. There was no proof of hallucinatory experiences, but occasionally she became intensely preoccupied with "thinking."

Helen had "always been a strange child," according to the family. She had been sensitive and idealistic, with poetic and musical tastes and talents, and had been ambitious to make a fine record. She had a brother and 2 sisters. The father was a hard, shrewd, successful manufacturer, of limited interests, very fond of the patient and disposed to favor her because she had shown more "ambition" than other members of the family. He had repeatedly and urgently taught her to be suspicious of boy friends or men who might show personal interest as a way of getting her money.

The patient has been continuously hospitalized since her first admission, and her subsequent course has been in the direction of narrowing interests and social deterioration. The history, clinical symptoms and course are not given in further detail here. The diagnosis of paranoid schizophrenia was unquestioned. She was for fourteen months at McLean Hospital, during which time one of us (J. C. W.) became well acquainted with her and accumulated many of her letters, which constitute the material of the present study. The spirit and style of

her letters, and some idea of her close preoccupation with the problem of affection, may be gathered, somewhat inadequately, from the following brief extracts:

From a letter to her father: "In spite of the fact of that you insist on exercising your patriarchal influence, my mind (even if not my pocket-book) is emancipated from that feudal conception of parental domination. No doubt you can arouse a certain amount of public sympathy from such narrow-minded goops as the Dovers and the Clarks, but it only goes to prove the futility of the development of intelligence and makes me realize that this is an unredeemable civilization of grocery men and fishmongers. Please do not count on me to worship your little idols with reverence. . . . Whatever cause you may find for malice or hatred toward me you may consider the outcome of your own will."

From a letter to a physician: "I think you are wonderful, but my life is completely futile and your kindness and effort is poured upon a dying plant."

Later, to the same physician: "Your meanness, ugliness and lack of any spiritual qualities at all make you appear to me only as an example of a horrible and hideous distortion of human nature. It is your hideous eye that I love now. I love it for all the suffering, all the misery, the loss of everything that it has brought into your ugly soul."

To the same physician two days later. "Honestly, darling, I love you with all my heart and soul. I want you so much that I ache with pain from wanting you—and then, I feel as though I cannot die soon enough. This hecticness is not doing me any good. I beg you to either love me or kill me."

To another physician: "I suppose you will call me good if I act like a tombstone. Well, every one learns by experience, and it is so unpleasant to have you repulse me that I shall eradicate all my tender feelings into a process of mockery. You may be very sure that I will never exhibit my affection for you again."

In view of the systematic distortion of the language pattern revealed in the statistical study of this patient's letters, it is of some interest to note certain semantic distortions involved in her "conspiracy delusion." This paranoid formation, offered by Helen rather defiantly at the time of admission, became more understandable when she elaborated it and discussed it more fully at a later time, when she was in fair rapport with one of the physicians. In brief, it then came out that what she "really meant" was that the persons in the so-called conspiracy would, by their beliefs and statements, "make her out" to be a prostitute on the basis of her actual behavior. The essence of the coercive "plot," which she so much resented, was so to speak, a classificatory plot—a broad general tendency, shared by many, to classify her as immoral—whereas she had believed, or tried very hard to believe, that her few sexual experiences had been of a poetic character—"a worshipful experience in the temple of artistic living." Captivated by a figure of speech and solaced thereby somewhat for the chagrin and disappointment of being "brushed off," Helen dramatized for herself this crusading role against the conventions, and, disdaining explanations to others (and clarification thereby to herself), she had included much more in her "plot" theory than she "really meant."

Another example of the same tendency to lump together too many meanings in one form of expression may be cited. One of Helen's favorite words was "insidious." In many of her earlier statements the term could be understood in its regular dictionary meaning, implying deceptive attack, ambush or treachery, but it gradually appeared, as one heard her use the word in many different contexts, that she meant by it anything malicious or hostile. In fact, when she finally was questioned about it, she said she had never appreciated that the word had any implication of concealment. Indeed, like many another sophomoric adolescent, Helen had a line of favorite words, similarly overworked and overextended in meaning, for example, "emancipated," "unredeemable" and "futility." In accord with her idealism and her concern about making a fine impression, her line was precious, rather than slangy. In this regard she was out of step with most of her contemporaries.

In figure 5 we present an analysis of the whole and of parts of a total of 50,000 (actually 49,991) running words in fully inflected form as they appeared in the successive letters of Helen B. These letters, being intimately personal, show in this graphic analysis the usual top concavity expected in such discourse, but the graph then becomes very straight and steep. Curve *I* represents the total sample of 50,000 words; curve *II*, the last 30,000 words; curve *III*, the first 20,000 words; curve *IV*, the first 10,000 words; curves *V* and *VI*, the second and the first 5,000 words respectively, and curves *VII* and *VIII*, the first and the third 2,000 words respectively.

Passing over the top concavity, one notes that all eight curves after about rank 10 descend at a slope that is steeper than the standard slope of *A* and *B*.

Hence one may say they are all "pulled" more by the autistic (I) pole of the vertical axis than by the social (U) pole of the horizontal axis. That is, in all eight lines the tendency to repetitiousness is greater than the tendency to diversification for all words except about the first 10 words in the top concavity. Hence these curves illustrate the type of distortion of word frequency predicated under the preceding discussion of autism.

But that is not all. Below the top concavity all eight lines are strikingly straight. The straightness means that the entire sample (except for the top concavity) is systematically balanced throughout, although on a different slant than the normal. The eight lines are also strikingly parallel. The parallelism means consistency. Helen is not merely autistic in tending more toward repetitiousness

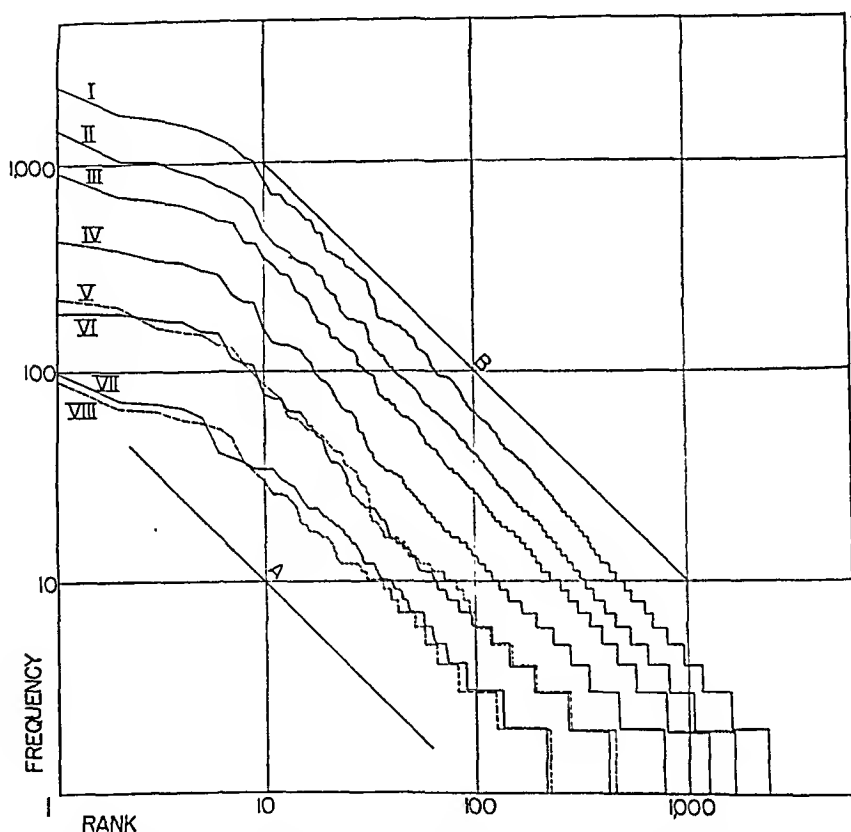


Fig. 5.—Rank-frequency distributions of Helen B. (with paranoid schizophrenia) in samples of (I) 50,000 words; (II) 30,000 words; (III) 20,000 words; (IV) 10,000 words; (V and VI) 5,000 words, and (VII and VIII) 2,000 words.

than toward diversification—she is systematically and consistently so, even to the point of rigidity.

Of course, in the interpretation of the steepness of any particular slope, there are certain general matters which must also be taken into consideration and which we mention here in order to show that we have not ignored them. Thus, in the equation $R \times F = C$, the size of C imposes restrictions on the numerical value of R , and therefore on the size of the vocabulary. These restrictions are not imponderable and have been explored in considerable detail elsewhere.¹⁴ For the purposes of the present paper, it suffices if we summarize the problem by stating that there is a limit beyond which F will tend to exceed the maximal R and the slope will become steeper than an equilateral hyperbola. Just how large a sample

should normally be required to exhibit this limitation depends on many factors.¹⁴ Presumably, it varies with the education and the social conscientiousness or tact of the speaker or writer. There are indications in the charts of the 3 patients presented here that with increasingly larger samples, up to about 50,000 words, the slope becomes little by little a bit steeper; that is, graphically the curves tend to converge a bit toward the bottom. Yet James Joyce, in "Ulysses," reached a bulk of 260,430 words (with a vocabulary of 29,899 different words) without deviating significantly from the equilateral hyperbola, except for a slight "top concavity." However, for the explicit purpose of this paper it is significant that a steep straight slope characterizes even small samples of Helen's speech production, even in the case of the 5,000 and 10,000 word samples.¹⁶

DISTORTION OF MEANING

In continuance of our discussion of the implications of the curves in figure 5, we must conclude that their straightness and parallelism may well be connected with a systematic distortion of meanings. To show why this distortion is likely, we may approach the problem circuitously by inspecting the meanings of words in normal speech. In general, the allocation of meanings to words must be orderly in the sense that the allocation is governed primarily by a subtle balance between the various needs of actual living. The resultant speech practices are reflected in the statistical word distribution, normally in the form of the hyperbolic equation. One of us (G. K. Z.)¹¹ has discussed in some detail elsewhere the principles of dynamic philology by which this equilibrium is maintained, or is restored, through linguistic and semantic change. In the present paper we merely refer briefly to some of the reasons for taking this hyperbolic equation as the mathematical expression for the optimal compromise between a tendency to repetitiousness and a tendency to diversification. (This theme will be developed further elsewhere⁷). We may point out here, however, that, according to this conception, whenever the relative frequencies of words do not meet the requirements of this equation, the stream of speech is not organized according to a maximum economy of effort.

If a man wants to buy a horse, his verbal pursuit of this equine objective will entail the use of those meanings which relate to horse buying, with the result that the words which possess those meanings will suddenly be used with a relative frequency that is considerably above average. One cannot know in advance whether this above-average frequency, in conjunction with the other parts of his discourse, will automatically meet the requirements of the hyperbolic equation. It may, or it may not. Similarly, any topic of special sustained preoccupation, in the actual world or in the world of fantasy, opens possibilities of disturbing the frequency distribution of words. In order to reorganize speech, in case such disturbance does occur, a reallocation of words and meanings is to be expected. Semantic changes, i. e., changes in the meaning of words, and linguistic changes, i. e., changes in the form of words, are mechanisms which restore and preserve this balance, so that the wieldiness of a small vocabulary can be preserved without undue sacrifice in precision of reference.

But without a discussion of the mechanism of linguistic and semantic change,¹⁷ it should be remembered that no change in word form or in word meaning is socially useful unless it is both understood and accepted in the speaker-auditor group in

16. In its mathematical implications the 45 degree slope of the equilateral hyperbola is a critical value, for with the steeper slopes the summation of the implied harmonic series of ratios becomes convergent, rather than divergent. This point has been further elaborated by one of us (G. K. Z.) and will be reported in a subsequent publication.⁷

17. Zipf,¹¹ pp. 20-39 and 274-278.

which the words and meanings are employed.¹⁸ The establishment of a balance, then, between word frequencies and meaning frequencies, in order to make speech more economically effective is not only a subtle philologic problem involving the operation of linguistic and semantic changes; it is also a difficult social problem, since it involves the making of only those changes which are socially acceptable.

But it does not follow that semantic and linguistic changes can occur only when they are socially acceptable. On the contrary, it is the speaker who selects both his words and his meanings and the auditor who tries to fit the selection into the patterns of his own experience. If the speaker does not make his selection clear—and every person has difficulty at times in expressing himself—it is the auditor who fails to understand and who thus forces the speaker to a greater semantic precision if he is to be comprehended.¹⁹

Of course, if the speaker is autistic, and therefore by definition disposed to sacrifice the auditor's convenience to his own, then the force of the auditor is diminished in its influence on the speaker's semantic and linguistic changes. With this diminution of the auditor's influence, the autistic person can save much effort in his speech by using more freely the mechanisms of semantic and linguistic change in which meanings and words are altered, coined or eliminated. Yet neither the desire to economize in speech nor the use of semantic or linguistic changes are in themselves abnormal. The abnormality of the autistic person lies only in ignoring the other fellow; that is, it lies in his disregard of the social obligation to make only those changes which are socially acceptable in the sense that they are both understandable and serviceable in the group.

Naturally, once the autistic person pursues his own linguistic and semantic paths of least effort, the result may well appear to his perplexed auditor as a disorder of meanings, or even as a disorder of association. Yet the autistic speaker in making his own language, without the nuisance of satisfying the auditor's needs, may employ the same principles of linguistic and semantic change as does the normal person, though not with the same care to insure community acceptance.

It is not difficult to fathom the impulse of the autistic person toward establishing his own meanings. Standard speech is often enough arbitrary and nonsensical in its symbolization. An odd assortment of meanings is frequently subsumed under one word, such as "the rose," "I rose," "my daughter Rose," or "I bear," "the bear," "bare legs." To be born into a world in which people use words in this fashion is clearly to be born into a verbally illogical world. But the world is not merely verbally illogical; to the autistic person it is "coercively" so, since he must both accept the verbal nonsense and play ball with it as a prerequisite of participating in society. Illogicality is wasteful of effort; logic is recommended for its economy of mind. The language of mathematics and natural science is recommended on the grounds of a greater logicity, though of course explicit definition or empiric verifiability are offered to the "other fellow" so that he may follow. Designers of artificial international languages, such as Esperanto, openly proclaim the need of a greater logic of speech for the sake of an easier understanding among people; yet these persons, too, labor scrupulously on explicit definitions so that the "other fellow" will be both able and willing to understand. However, in view of the labor of explicit definition, and the like, which is required by the need for a social understandability of language, one can see how an autistic person, in dodging the effort, not only becomes freer but needs to work less in devising his new and more logical language.

18. A semantic change is socially serviceable when it saves more effort in expression than would be the case without the change. The same applies to linguistic change.

19. For a more detailed discussion, see Zipf,¹¹ pp. 212-215.

Any one can build a new language that is more consistent if he ignores the "other fellow." For example, given the word "tune," meaning a "kind of noise," then "Neptune" is the kind of noise that Nep makes; if this "noise" is the surf, then Nep is the sea. And as with the morpheme tune, so, too, with other morphemes. Given the words "cat" and "catnip," one can see how catnip may nip the cat. It can be seen that "mother" and "smother" are related, that "smother" may mean "to be nice to babies" or that "it isn't really catnip, because you see that cats like it."²⁰

One clever, subtle and secretive paranoid woman known by one of us (J. C. W.) used to speak with a smile of "airplane messages." At least that was the way the auditors always understood, or rather misunderstood. The nurses even watched for airplanes flying over to see how she took the messages. One day she condescended to explain her meaning. The term was "air-plain messages," meaning "plain as air," a meaning that was, in fact, not plain at all except to the initiated, for air signifies to the uninformed practically nothing, and even the existence of air as a substance is only appreciated through subtle and involved experimentation. Hence, "air-plain messages" are the very reverse of "plain" and require extraordinary subtlety for their apprehension. It is of some interest, in this connection, that this same patient devised a special secret alphabet in which she used to write or draw on large sheets of paper a whole "newspaper" with headlines and display advertisements and a society column, all for her sole and secret enjoyment.

In thus fabricating a new language, the autistic person is not necessarily confusing the word with reality any more than is the person who coined the words "lockjaw," "can opener" or "fireplace." Nevertheless, to be arbitrary and individualistic in selecting what is to be named in all of experience, and how it is to be named and how it is to be compared generically with other named things, is ineffective if one wants the advantages that accrue to social life.²¹ The distortion of meanings represents an economy of mind, but it is an autistic economy that remains radically different from that of normal social speech.

If we return now to the case of Helen B., we may say that the appearance of this autistic characteristic in the speech of this patient with paranoid schizophrenia, as expressed in the steep, straight slope of her speech curve, leads us to a certain problem that is connected with our previous tool analogy. After all, the uses of words and the uses of tools are analogous. We may ask, therefore, whether the autistic trend in speech usage, with its distortion of meaning, is but a particular manifestation in the speech process of a general difficulty in handling all kinds of tools, including word tools. In short, does a schizophrenic person have difficulty in using hammers, nails, saws and masses of materials? Does he try to alter autistically the uses of tools and materials? Does he try to rearrange their uses in accordance with his own point of view? If he does, he may run into difficulties with the actual world.

According to the observations of Cameron,²² reported in a brilliant paper on schizophrenic thinking in problem solving, the schizophrenic person shows an overinclusion of environmental and imaginal material in the problem itself. Thus, there seems to be a resistance to the acceptance of the tester's delimitation of the problem. Moreover, the schizophrenic subjects called for "changes in the rules

20. Much will depend on the particular morphemes selected as the fundamental units on the basis of which the "more logical" language is developed.

21. For discussion of a word as a name of a frequently used category of experience, see Zipf,¹¹ pp. 267-271.

22. Cameron, N.: Schizophrenic Thinking in a Problem-Solving Situation, *J. Ment. Sc.* 85:1012-1035, 1939.

of procedure and in the materials, and declared the situation to be inadequate instead of themselves." Cameron reported:

Generalizations were numerous; and shifts from one hypothesis to another occurred without evidence of an unusual difficulty. The generalizations were unsuccessful [in solving the problem as set by the tester] because they were (a) too broad, (b) too involved, or (c) too entangled with personal problems and phantasies, or (d) because the language structure was so disorganized that it could neither function as social communication, nor serve as a basis for the patient's own performance. Moreover, (e) the generalizations, even when quite correct, often did not lead to any corresponding act.²²

In short, the patients had trouble in organizing materials and conceptual tools. The patients' "distortions" of material and situation seem to have been comparable to "distortions" of word usages.

SUMMARY

1. We have shown that in standard language usage the frequency of occurrence of the different words in a given sample is mathematically related to the ranks of the words when arranged in order of decreasing frequency, this mathematical relation being a close approximation to an equilateral hyperbola.

2. Utilizing this criterion, by means of its straight line expression on logarithmic graphs, we have studied the language behavior of a child (reported by Uhrbrock) and also the speech production of 3 psychiatric patients with different types and durations of psychoses, as exhibited in spontaneously written personal letters. We found that the curves for all subjects approximated roughly the equilateral hyperbola but that certain significant deviations therefrom characterized the different subjects.

(a) In the intimate personal letters of the patients (as also in considerable control material from personal letters of normal persons) the 10 most common words (essentially articulatory words) were used with considerably less frequency than in more formal discourse directed toward several persons, probably because there was less need for explanatory and definitive terms. This phenomenon was shown on the graphs by a bend toward the left at the top, here called the "top concavity."

(b) The child's language production curve was characterized by a slight general concavity, or slightly bow-shaped distribution, the bend (or region of greatest excess frequency) occurring about the region of words of the thirtieth or fiftieth rank.

(c) One of the patients, who had a brief schizoaffective type of illness, and who has shown before, during and after her psychotic periods a childishly dependent attitude toward parent surrogates, showed in her language behavior graphs a slight general concavity comparable to that of the child, with the principal bend occurring usually about the region of the fiftieth to the one-hundredth rank. This patient's graph showed also a consistent downward bend at ranks 11, 12 and 13.

(d) A paranoid patient showed in his language behavior some small irregular deviations, not very constant from one sample to another.

(e) A patient with paranoid schizophrenic psychosis showed in her language behavior graph a rigidly systematic deviation from the normal curve in the direction of a consistent, straight and uniform steepness, interpreted by us as an expression of an autistic speech tendency.

3. As a tentative working hypothesis, we have interpreted our data in terms of opposing tendencies to repetitiousness and to diversification, which we have derived from considerations of economy and convenience; the tendency to repetitiousness tends to increase frequency of use and to diminish the number of dif-

ferent words, whereas the tendency to diversification tends to increase the number of different words and to diminish the relative frequency, the net resultant being a relatively steady proportionality, represented in the equilateral hyperbola. These two hypothetical tendencies have further been illustrated in terms of an analogy with a set of mechanical tools, and our quantitative data have been interpreted in the light of these tendencies and this analogy.

4. We have indicated the hypothetical possibility that these two tendencies are equivalent to the consideration of egocentric and allocentric convenience respectively. When we interpreted this type of verbal egocentricity as autism, we found that the material of the patient with paranoid schizophrenia was definitely autistic as compared with all the other material presented.

5. We have further pointed out how an autistic person could go astray into a distortion of meanings by employing the normal mechanisms of linguistic and semantic changes for his own ease, without bothering to meet the normal prerequisite of a social serviceability and a social understandability as necessary for all linguistic and semantic innovations, and that he might then find himself thereby verbally and conceptually handicapped in attempting to solve "neutral problems" set by a tester, and also in dealing with real problems in an actual world.

ORAL AND INTRAVENOUS DEXTROSE TOLERANCE CURVES OF PATIENTS WITH MANIC- DEPRESSIVE PSYCHOSIS

E. F. GILDEA, M.D.

V. L. McLEAN, B.A.

AND

E. B. MAN, PH.D.

NEW HAVEN, CONN.

There are many reports in the literature demonstrating wide variations in oral dextrose tolerance curves for "normal" persons.¹ Similar variations when found in mentally ill patients continue to be called abnormal in the psychiatric literature.² McFarland and Goldstein³ have reviewed most of the older literature, and such a survey will not be repeated here. Recently Lozner, Winkler, Taylor and Peters^{1a} have reemphasized the variations in oral dextrose curves and suggested that much of the controversy concerning tolerance for carbohydrate in specific diseases would be resolved if a standard intravenous test were universally adopted. The present report is concerned with a reinvestigation of the values for intravenous dextrose tolerance curves of 30 patients with manic-depressive psychosis. For 19 of these patients a comparison of the curves following the oral and the intravenous administration of dextrose has been made.

METHODS AND MATERIAL

The procedure for the intravenous dextrose tolerance test was essentially the same as that employed in the experiments of Lozner, Winkler, Taylor and Peters.^{1a} Patients were in a postabsorptive state. After the fasting blood sample was taken, 50 cc. of a 50 per cent solution of dextrose was injected intravenously during a period of five minutes. After this, samples of blood were taken at intervals timed from the end of the injection.

In the oral tolerance tests the patient either drank or was given by stomach tube 250 cc. of a solution containing at least 50 Gm. of dextrose. If the subject weighed more than 50 Kg., 1 Gm. of dextrose per kilogram of body weight was ingested.

From the Department of Psychiatry, Yale University School of Medicine.

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As in the investigation of Lozner, Winkler, Taylor and Peters,^{1a} the blood proteins were precipitated by the Somogyi zinc sulfate method,⁴ and the filtrate was analyzed for the sugar content by a modification of Benedict's macromethod⁵ with the use of Rothberg and Evans' tubes.⁶ Usually three or more days were allowed to elapse between repeated oral and intravenous tests.

The patients were fed ward diets which contained considerable amounts of carbohydrate, but were adequate also in fats, proteins and vitamins. In some cases tube feedings were necessary to maintain caloric intake. Attempts were made to alter the oral dextrose curves by high fat diets. The patients complained so bitterly that the diets were not continued for more than two weeks.

The behavior of each patient, particularly with regard to mood and amount of activity, was studied, and an attempt was made to correlate these observations with the variations in the dextrose tolerance curves. The underactive patients were kept in bed during the test, except for a brief trip to the toilet if requested. Most of the agitated patients also remained in bed, but a few manic or very agitated persons were allowed to pace about in their rooms. All the patients were severely ill, being sufficiently depressed, manic or agitated to require special nursing care in order to prevent suicide or to control overactivity.

DATA

In figure 1 the intravenous dextrose tolerance curves are compared with the data of Lozner, Winkler, Taylor and Peters.^{1a} The upper and lower solid lines represent the maximum and minimum values for 60 normal subjects studied by them, except for the values at the second and third hour intervals after administration of dextrose, when their statistical figures for the normal range were employed. In evaluating their results for the patients, these authors treated their data for the two hour interval statistically. Instead of using maximum and minimum values, they considered as outside the normal range any individual value differing from the mean normal value by an amount greater than three times the standard deviation. Two hours after administration of dextrose their mean value was 78.8 mg. per hundred cubic centimeters, with the standard deviation ± 7.2 mg., 65 to 99 mg. per hundred cubic centimeters being considered as the statistical normal range. If only minimum and maximum values are used as criteria, the normal range would be 65 to 90 mg. per hundred cubic centimeters. Three hours after administration of dextrose the minimum value was 67 mg., the maximum value 81 mg., the arithmetical mean 75.5 mg., the standard deviation ± 5 mg. and the statistical normal range 60 to 91 mg. per hundred cubic centimeters.

In figure 2 oral dextrose tolerance curves are compared with the data of Friedenson, Rosenbaum, Thalheimer and Peters.^{1b} The lower and upper solid lines represent the minimum and maximum values for their 10 subjects after the ingestion of 50 Gm. of dextrose, except for the maximum value two hours after administration of dextrose. With the exception of a blood sugar of 125 mg. per hundred cubic centimeters for 1 subject, the maximum value was 88 mg. per hundred cubic centimeters. Foster⁷; Gilbert, Schneider and Bock,⁸ and Hamman and Hirschman⁹ found that the sugar level of venous blood usually returns to normal two

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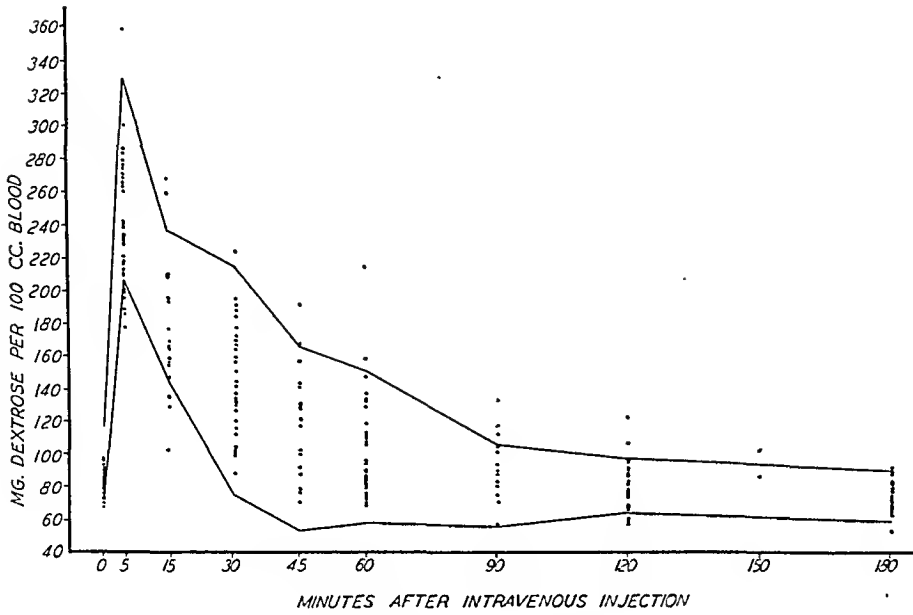


Fig. 1.—Intravenous dextrose tolerance curves. The upper and lower lines represent the extremes of the blood sugar levels for 60 normal persons studied by Lozner, Winkler, Taylor and Peters.^{1a} At the intervals of two and three hours after administration of dextrose, statistical values for normal ranges were employed; at other intervals maximal and minimal figures were used.

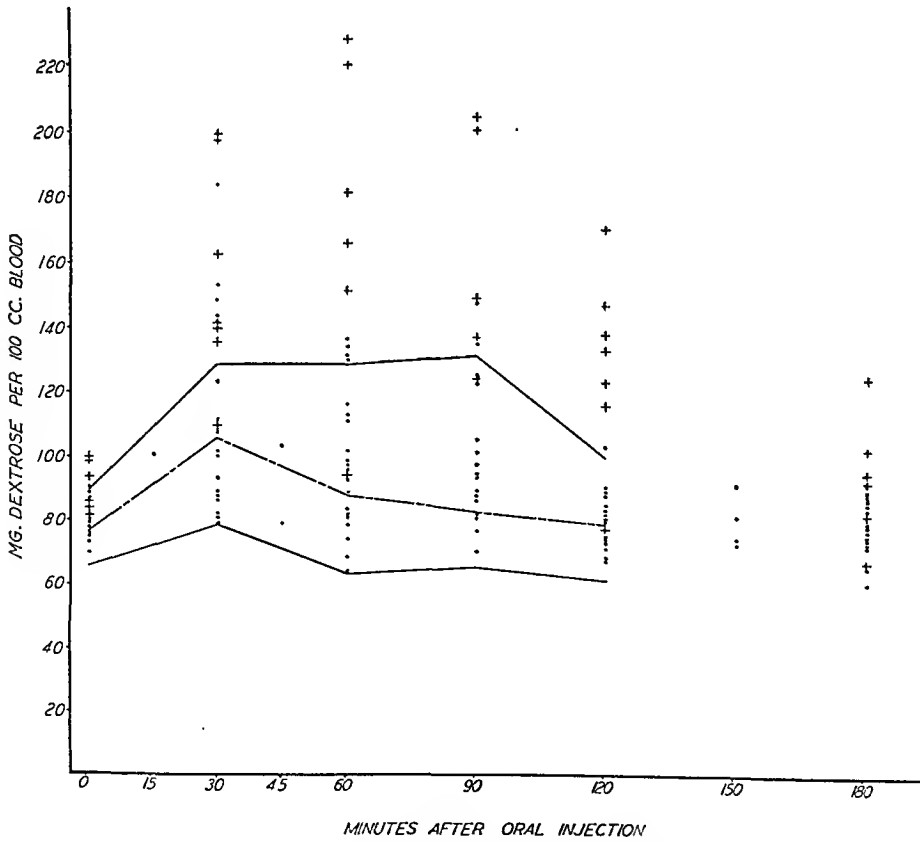


Fig. 2.—Oral dextrose tolerance curves. The upper and lower lines represent maximal and minimal values and the broken line average values obtained by Friedenson, Rosenbaum, Thalheimer and Peters.^{1b} The crosses (+) represent values for subjects with a prolonged curve.

hours after the administration of dextrose. It would seem, therefore, that a sugar content of 100 mg. per hundred cubic centimeters of blood would best represent the maximum level two hours after the administration of dextrose, and this value was used in drawing the normal curve.

It is usually considered that the blood sugar rises at least to 130 mg. per hundred cubic centimeters at some time after the ingestion of dextrose. In Foster's ⁷ studies there was a definite increase in blood sugar. Gilbert, Schneider and Bock ⁸ found the maximum rise between fifteen and forty-nine minutes after the administration of dextrose. Although the minimum line on the graph agrees with the data of Hanman and Hirschman,⁹ the low values are uncommon for normal persons during the first hour of an oral dextrose tolerance test. The average values found by Friedenson, Rosenbaum, Thalheimer and Peters,^{1b} which are represented on the graph by a broken line, probably constitute the "normal" response to ingestion of dextrose. In the figure, crosses (+) have been used to designate the oral blood sugar values which remained high for longer than the normal time.

In the table are given the data on patients for whom both an intravenous and an oral dextrose tolerance curve were obtained. For 1 subject (patient 18) two oral but no intravenous studies were made. The psychotic state of each patient during hospitalization is noted briefly in the column at the right. Only 1 subject (patient 18) showed pronounced changes in clinical symptoms at the times of two different dextrose tolerance tests; therefore no attempt has been made to describe the exact state of the patient on the day of each test. The patients are arranged in groups. In group I are 4 patients with normal oral and intravenous dextrose tolerance curves. In group II are 11 patients, 10 of whom had flat oral curves; the last 5 patients had rapid diminution of the blood sugar after intravenous injection of dextrose. In group III are 5 patients with prolonged oral dextrose tolerances. The flat curves are designated by *F*, and the prolonged curves by *P*. The table does not include data on intravenous dextrose tolerance tests performed on 11 patients who did not also have oral dextrose tolerance tests. However, the results of all intravenous dextrose tolerance tests have been included in figure 1.

RESULTS

Thirty-four intravenous dextrose tolerance curves were studied for 30 patients with manic-depressive psychosis. Dots represent the sugar values determined at intervals after the injection of dextrose. As can be seen in figure 1, in 32 of the 34 curves taken one hour after the injection of dextrose the blood sugar values were within the minimum and maximum ranges for normal subjects, i. e., between 70 and 148 mg. per hundred cubic centimeters of blood. In this figure, as well as in figure 2, it is impossible to designate the total number of determinations at any given time because frequently two or three determinations of the blood sugar on different patients gave identical results.

For only 24 of these curves were determinations of the blood sugar made two hours after the administration of dextrose. In 19 of these 24 curves the sugar values were within the normal range of 66 to 99 mg. per hundred cubic centimeters. Three curves (patients 16, 8 and another not indicated in the table) showed values below and 2 curves above the normal range. These high values (not included in the table) were found in the 2 patients who had blood sugars above the normal range one hour after administration of dextrose. Both these patients had symptoms of overactivity of the thyroid, with which a prolonged rise in blood sugar is often associated. On the whole, the data indicate that the removal of dextrose from

Dextrose Tolerance Curves for Twenty Patients Who Had Both Intravenous and Oral Tests

No.	Sex	Age, Yr.	Date	Oral or Intra-venous Test	Pro- or longed Flat Curve	Blood Dextrose Level at Minutes Indicated After Administration of Dextrose										State
						0	5	15	30	45	60	90	120	150	180	
						Mg. of Dextrose per 100 Cc. of Blood										
						Group I: Both Curves Normal										
1	M	33	11/ 6/33	O	..	75	144	...	130	88	78	..	78	Depressed
			11/13/33	Iv	..	80	263	194	164	117	91	..	84	
			12/18/33	O	..	80	81	...	113	94	83	..	82	
2	F	24	12/21/33	Iv	..	87	187	158	120	102	90	95	..	75	67	Depressed; agitated
			11/14/33	O	..	77	149	...	78	
3	F	27	11/28/33	Iv	..	80	198	169	111	...	73	82	66	..	67	Depressed
			11/27/33	O	..	81	109	...	111	
4	F	34	12/ 5/33	Iv	..	81	210	177	145	...	110	91	77	..	68	Depressed
			11/ 1/37	Iv	..	78	206	164	149	129	110	126	88	92	88	
			11/ 4/37	O	..	79	112	...	137	
Group II: Flat Oral Curves (Except No. 12)																
5	F	21	9/12/33	O	F	78	102	...	79	83	82	..	81	Manic
			9/28/33	O	F	87	102	...	93	88	76	..	61	
			10/26/33	Iv	..	74	191	...	120	...	89	..	69	..	68	
6	M	18	11/ 2/33	O	F	82	81	...	74	..	85	..	85	Manic
			11/ 7/33	Iv	..	85	233	83	70	92	..	90	
7	F	22	10/10/33	O	F	75	103	73	..	73	Manic
			10/17/33	Iv	..	86	274	92	81	79	..	76	
8	M	41	10/12/33	O	F	70	78	...	84	81	58	..	51	Depressed; agitated
			10/24/33	Iv	..	88	358	94	98	90	..	90	
			11/21/33	O	F	81	80	...	90	93	90	..	87	
			12/14/33	O	F	89	...	157	88	...	107	..	78	..	76	Depressed
9	M	19	12/21/33	Iv	..	85	196	...	132	...	83	..	81	..	80	Depressed
			11/20/33	O	F	77	93	...	90	..	72	..	75	
10	F	41	11/23/33	Iv	..	83	200	144	136	...	64	70	81	
			12/19/39	O	F	79	82	...	75	72	83	
			12/21/39	Iv	..	75	268	...	135	...	82	88	76	
11	M	30	1/18/40	O	F	73	...	101	87	79	
			11/ 4/33	O	F	79	101	76	70	85	..	84	76	Depressed; agitated at times
			11/ 9/33	Iv	209	...	123	...	97	
12	F	25	11/14/33	O	..	84	231	103	88	70	73	98	76	Depressed
13	M	24	12/12/33	Iv	F	81	101	...	102	98	77	
			12/14/33	O	..	82	212	193	103	97	84	93	91	..	88	Depressed; apathetic
14	M	60	12/19/33	O	F	80	87	...	89	
			12/20/33	Iv	..	80	212	129	99	96	87	90	79	..	77	Depressed
15	F	30	1/ 3/34	O	F	77	102	...	96	
			1/ 4/34	Iv	176	135	102	88	72	
Group III: Prolonged Oral Curves																
16	F	29	9/12/33	O	F	70	88	...	135	100	..	73	74	Manic
			9/28/33	O	F	84	110	...	162	148	78	..	68	
			10/19/33	O	F	86	110	...	162	148	116	..	93	
17	M	64	10/24/33	Iv	..	96	286	76	..	61	..	67	Depressed; agitated
			9/19/39	O	..	93	164	...	182	163	188	..	93	
			9/21/39	Iv	..	93	260	...	178	...	148	..	63	..	81	
18	F	33	11/14/39	O	F	93	142	...	167	..	147	..	103	
			10/ 7/37	O	..	100	196	...	221	206	169	..	125	Depressed
19	M	57	8/20/38	Iv	..	93	184	...	117	78	67	..	01	Depressed; agitated
			9/ 8/38	O	..	98	218	...	161	...	133	114	133	..	72	
20	M	57	10/10/39	O	F	82	200	...	229	202	133	..	83	Depressed
			10/17/39	Iv	..	88	136	123	..	91	
			10/17/39	Iv	..	88	231	...	131	...	81	82	78	..	79	

the blood is not retarded in patients with manic-depressive psychosis. It made no difference whether the patients were manic or depressed or had agitated depressions. Of the 30 subjects, 6 were manic, 18 were depressed and 6 had agitated depressions.

Inspection of the intravenous dextrose tolerance curves suggests that the removal of dextrose from the blood stream may sometimes be accelerated in patients with manic-depressive psychosis. Five of 28 patients (the last patients in group II of the table) had blood sugar values at or below 105 mg. per hundred cubic centimeters thirty minutes after the administration of dextrose. In the studies of Lozner, Winkler, Taylor and Peters,^{1a} only 7 of 52 normal subjects had a sugar content below 105 mg. per hundred cubic centimeters of blood one-half hour after the administration of dextrose. Three patients, none of whom was identical with the 5 patients with low sugar values one-half hour after administration of dextrose, had blood sugar values of 58, 59 and 61 mg. per hundred cubic centimeters two hours after administration of dextrose, values below the minimum level of 65 mg. per hundred cubic centimeters. No specific symptom accompanied the rapid fall in blood sugar of these 8 patients. Patient 16, a woman aged 29, was so overactive and manic that she had to be placed in a dry pack for each venipuncture; patient 12, a woman aged 25, was depressed and somewhat agitated, and patient 14, a man aged 60, was depressed and apathetic. Patient 11, a man aged 30; patient 8, a man aged 41; patient 13, a man aged 24; patient 15, a woman aged 30, and a woman aged 29, not indicated in the table, were cooperative but depressed. None of these patients had a notable loss of weight before the dextrose tolerance tests were made.

In figure 2 are graphically represented 30 oral dextrose tolerance curves for 20 patients with manic-depressive psychosis. As indicated in the table, of these 20 patients, 4 were manic, 10 were depressed and 6 had agitated depressions. Their symptoms bore no relation to the behavior of the oral dextrose tolerance curve. In this figure it can be seen that 6 patients, two hours after administration of dextrose, had sugar values between 116 and 169 mg. per hundred cubic centimeters, a distinct elevation above 100 mg. per hundred cubic centimeters. In the last section of the table are grouped the data on 5 of the patients who showed these prolonged curves, including a curve for patient 16, for whom the maximum rise to 136 mg. per hundred cubic centimeters did not occur until an hour and a half after the ingestion of dextrose. Of these subjects, patient 17 was a man 64 years of age. Since a prolonged increase in blood sugar sometimes obtains in elderly patients, little significance can be attached to the two prolonged oral dextrose tolerance curves for this patient.

All 5 subjects, except patient 16, had been admitted to the psychiatric wards more than three days before the tolerance tests were performed and had eaten at least fairly well during the forty-eight hours before the test. Patient 16 was admitted only twenty-four hours before the initial normal oral dextrose tolerance test. She was talkative and overactive and so uncooperative that it was necessary to administer the dextrose by stomach tube. However, the oral curves for this patient which were prolonged were obtained on subsequent dates, September 28 and October 19, when the patient had been hospitalized for some time and after daily special feedings had been administered. The prolonged curves, therefore, cannot be considered as due to carbohydrate deficiency prior to the dextrose tolerance test.

It is apparent from the data in the table that all 4 patients who had prolonged oral dextrose tolerance curves and were studied with both oral and intravenous tests did not have prolonged intravenous curves, in spite of prolonged oral curves.

The length of the oral curve is therefore attributable to irregularities in absorption of dextrose from the gastrointestinal tract, rather than to impairment in the removal of dextrose from the blood stream.

Of the 4 subjects (patients 16, 17, 18 and 20) who had prolonged oral dextrose tolerance curves and on whom more than one oral test was made, only 1 (patient 18) had symptoms of clinical improvement at the time of the final oral dextrose tolerance test. This oral curve when she was improved, was normal; the earlier oral curve, when she was seclusive and depressed, had been prolonged.

In contrast to the prolonged oral dextrose tolerance curves, 10 patients had 14 "flat" oral tolerance curves (table). This fact can be observed graphically in figure 2 by noting the number of determinations which fell below the average values found by Friedenson and associates¹⁰ one-half and one hour after the ingestion of dextrose. These low values corroborate the foregoing conclusion that in the manic-depressive patient removal of carbohydrate from the blood stream is not retarded.

COMMENT

The absence of prolonged intravenous dextrose tolerance curves for manic-depressive patients was somewhat unexpected because earlier oral tests on such patients had not infrequently yielded prolonged curves. This observation is, however, in accordance with the data of Bowman and Kasanin¹⁰ and of Whitehorn.¹¹ These investigators found that in patients with mental disease the fasting blood sugar was usually within normal limits. This was true even when the patients exhibited symptoms of profound emotional excitement.

Of the 5 patients in this series with prolonged oral dextrose tolerance curves, 1 (patient 16) was given paraldehyde on the evenings before the tests on September 28 and October 19. One may think of the possibility that such sedation delayed absorption of dextrose from the gastrointestinal tract. We are not aware of any clinical experience or note in the literature with respect to the effect of paraldehyde on the motility of the gastrointestinal tract.

Since the other 4 patients with prolonged oral dextrose tolerance curves had barbiturates on the evenings preceding some of the tests and no sedation at other times, the length of the curve does not seem to be associated with the use of these drugs. To be specific, patient 19 had no sedation, and patient 17 had 10 grains (0.65 Gm.) of barbitol the evening before September 19 and no sedation the evening before November 14, although the tests on both these days gave prolonged curves. Patient 18 had no sedation the evening before the prolonged curve was obtained, but did have 3 grains (0.195 Gm.) of sodium amytal on the evening before the normal curve was taken. Patient 20 had 10 grains (0.65 Gm.) of barbitol each evening before the test.

In discussion of the results, it was stated that 3 patients, 8, 16 and another, had blood sugar values of 58, 61 and 59 mg. respectively per hundred cubic centimeters two hours after the intravenous injection of dextrose. These are values below the minimum found for normal subjects—65 mg. per hundred cubic centimeters. Little emphasis can be placed on these 3 low values because Lozner, Winkler, Taylor and Peters¹² found occasional instances of hypoglycemia in normal subjects. These authors, as well as Wilder¹² also found that the three

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12. Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1940.

hour intravenous dextrose tolerance test was of limited value in the diagnosis of pathologic hypoglycemia. These 3 low values are of some interest, however, in connection with other observations. Five of 28 manic-depressive patients, but only 7 of the 52 normal subjects studied by Lozner and his co-workers,¹³ had blood sugars below 105 mg. per hundred cubic centimeters of blood one-half hour after intravenous injection of dextrose. Ten of 20 patients had flat oral dextrose tolerance curves. There may be a connection between these low blood sugars and the fact that an exacerbation of manic-depressive symptoms is usually accompanied by loss in body weight. However, our data are insufficient for the formulation of any definite hypothesis.

These spontaneous variations in oral dextrose tolerance curves were not prevented by standard diets. Soisalo¹³ has reported similar experiences. Variations in the oral curves did not correspond with any special disorder in emotional status. These observations are similar to those of Katzenelbogen and Muncie,¹⁴ but do not agree with those of Diethelm,¹⁵ who found some correlation between the character of the oral sugar tolerance curves and the patient's emotional status.

CONCLUSIONS

In none of the 34 intravenous dextrose tolerance curves obtained on 30 manic-depressive patients were high blood sugar values exhibited two hours after the intravenous injection of dextrose, except for 2 curves for patients who also had symptoms of overactivity of the thyroid. The 32 curves which were not prolonged demonstrate that the removal of sugar from the blood stream is not retarded in manic-depressive patients.

In 6 of 30 oral dextrose tolerance curves obtained on 20 manic-depressive patients, the sugar was elevated decidedly above 100 mg. per hundred cubic centimeters of blood two hours after the ingestion of sugar. These prolonged oral dextrose tolerance curves were observed for patients who had normal intravenous dextrose tolerance curves. It may be concluded that abnormal oral dextrose tolerance values for manic-depressive patients are attributable to delayed absorption of dextrose from the gastrointestinal tract and cannot be accepted as evidence of an intrinsic disorder of carbohydrate metabolism.

Yale University School of Medicine.

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SYNDROME OF INVOLVEMENT OF THE POSTERIOR CORD OF THE BRACHIAL PLEXUS

RUSSELL N. DE JONG, M.D.

ANN ARBOR, MICH.

The motor and sensory changes that result from most varieties of injury to the brachial plexus are well known. The clinical picture seen in the upper arm type of involvement, or Erb's paralysis, or the Erb-Duchenne syndrome, and that seen in the lower arm type, or the Dejerine-Klumpke syndrome, have been described on many occasions, as has total palsy of the brachial plexus. Less clearly defined, however, are those syndromes which may be produced by injury to the secondary divisions, or cords, of the plexus. Tinel¹ merely mentioned the possibility that these may be injured and stated that the syndrome of the posterior secondary trunk is characterized by complete paralysis of the circumflex and musculospiral nerves. Pollock and Davis² stated that lesions of the secondary cords are encountered infrequently and that injury to the posterior cord results in paralysis of the muscles supplied by the radial and axillary nerves. The clinical picture resulting from a lesion of the posterior cord (fasciculus posterior) is described in the following case.

REPORT OF A CASE

A business man aged 39 slipped and fell while walking across a log on a hunting trip. In attempting to break the fall, he struck the left shoulder against a pole and suffered an anterior dislocation of the shoulder. A wrist drop was noticed immediately. He consulted his local physician at once, and the shoulder was replaced. For two or three days the patient noticed severe pain in the region of the shoulder, but not after that. He continued to have weakness of the extensor muscles of the wrist and hand and also weakness of extension at the shoulder. He had slight loss of sensation over the lateral aspect of the upper portion of the arm. There were some swelling and increased perspiration of the hand.

On examination two weeks after the injury, the patient had complete paralysis of extension of the shoulder, elbow, wrist and fingers on the left side. The arm hung loosely at the shoulder, and there was loss of abduction and extension, of forward and backward movement and of both internal and lateral rotation of the shoulder. On attempts to abduct the arm the patient shrugged his shoulder and tilted his body to the right. He was unable to extend the forearm, wrist or fingers, and there was a complete wrist drop. There was weakness but not complete loss of grip. Abduction and extension of the thumb were absent. The hand was held in pronation, with definite weakness of supination. There was atrophy of the deltoid and posterior axillary muscles, and to a lesser extent of the triceps and the extensor muscles of the hand. The triceps, deltoid and radial periosteal reflexes were absent. The biceps reflex was active. There was a circumscribed area of anesthesia over the lateral aspect of the upper portion of the arm just below the shoulder, but no other sensory changes could be demonstrated. The fingers and hand were swollen, and the skin was moist and cyanotic.

The patient also showed evidence of secondary contractures and periarticular adhesions, both of the shoulder and of the hand. These were broken up by manipulation, with the patient under anesthesia, with resulting gain in range of motion, followed by slow, but progressive, improvement in function. When the patient was last seen, thirteen months after the injury, the principal residuals consisted of weakness of the extensor muscles of the fingers and thumb. There had been complete return of function in the muscles of the shoulder and the upper part of the arm, and the patient was able to extend the forearm and wrist.

From the Department of Neurology, the University of Michigan Medical School and University Hospital.

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2. Pollock, L. J., and Davis, L.: *Peripheral Nerve Injuries*, New York, Paul B. Hoeber, Inc., 1933, p. 400.

The posterior cord (*fasciculus posterior*) of the brachial plexus is supplied by fibers originating from the anterior rami of the fifth, sixth, seventh and eighth segments of the cervical portion of the spinal cord, and probably of the first dorsal segment. It is formed by fusion of the posterior divisions of the lateral (upper), middle and medial (lower) trunks of the plexus. From the posterior cord originate the thoracodorsal nerve (*nervus thoracodorsalis*), the upper and lower subscapular nerves (*nervi subscapulares*), the axillary nerve (*nervus axillaris*) and the radial nerve (*nervus radialis*). The upper, or short, subscapular nerve supplies the subscapular muscle, which brings about medial rotation of the humerus when the arm is vertical and draws forward the humerus when the arm is in abduction. The lower subscapular nerve supplies the *teres major* muscle, which extends and adducts the arm and rotates it medially; it also supplies part of the subscapular muscle. The thoracodorsal, or long subscapular, nerve supplies the *latissimus dorsi* muscle, which adducts and extends the humerus and rotates it internally. The axillary, or circumflex, nerve supplies the deltoid and the *teres minor* muscle. The deltoid muscle is the principal abductor of the humerus; it raises the arm to the horizontal position and also aids in forward and backward movement of the humerus. The *teres minor* muscle rotates the humerus laterally when the arm is in the vertical position and draws the humerus backward when the arm is in the horizontal position. It is an abductor and an external rotator. The axillary nerve also has a cutaneous branch, the lateral brachial cutaneous nerve, which supplies the skin over the lateral surface of the upper half of the arm.

The radial, or musculospiral nerve is the largest of the nerves which come off from the posterior cord of the brachial plexus and is in reality a continuation of the cord. It supplies the extensors of the forearm, wrist and fingers. The largest muscle which it supplies is the *triceps*, which is the extensor of the forearm on the upper part of the arm; it also acts to draw the entire arm backward. Functioning with the *triceps* and assisting it in extension of the forearm is the *anconeus* muscle. The radial nerve supplies the *brachioradialis*, or *supinator longus*, muscle, which flexes the arm and brings about slight supination, and the *brachialis* muscle, which is one of the flexors of the forearm, but the latter muscle derives its principal supply from the musculocutaneous nerve. The radial nerve supplies the extensor muscles of the wrist, hand and fingers, namely, the *extensor carpi radialis longus*, the *extensor carpi radialis brevis*, the *extensor digitorum communis*, the *extensor digiti quinti proprius*, the *extensor carpi ulnaris* and the *extensor indicis proprius*. The *extensor carpi radialis longus* extends the hand and brings about slight abduction; the *extensor carpi radialis brevis* is an extensor of the hand; the *extensor digitorum communis* extends the phalanges of the second, third, fourth and fifth fingers, and secondarily brings about extension of the hand; the *extensor digiti quinti proprius* causes extension of the little finger; the *extensor carpi ulnaris* causes extension and adduction of the hand, and the *extensor indicis proprius* extends the index finger. The *extensor pollicis longus*, the *extensor pollicis brevis* and the *abductor pollicis longus*, three muscles of the thumb, are also supplied by the radial nerve. The long abductor muscle causes abduction and slight extension of the thumb and abduction of the hand; the *extensor pollicis brevis* brings about abduction of the thumb and extension of the first phalanx, and the *extensor pollicis longus* brings about extension of the terminal phalanx and extension and slight abduction of the thumb. Finally, the radial nerve also supplies the *supinator* muscle (*supinator radii brevis*), which brings about supination of the hand. The cutaneous branches of the radial nerve are the medial brachial cutaneous, the posterior brachial cutaneous and the dorsal

antibrachial cutaneous, which supply areas over the arm and forearm areas which are also supplied to a certain extent by the ulnar and median nerves. The superficial radial nerve, through a lateral terminal branch, supplies portions of integument over the radial side of the thumb and the thenar eminence not supplied by other nerves of the forearm, and, through a medial terminal branch, supplies portions of the index and middle fingers which are also supplied by other cutaneous nerves.

COMMENT

In the case reported here there was evidence of involvement of the posterior cord of the brachial plexus. There were complete involvement of the axillary nerve, with paralysis of the deltoid and the teres minor muscle and paralysis of the subscapularis, the latissimus dorsi and the teres major muscle. As a result, there were loss of abduction, extension and internal and external rotation at the shoulder and loss of forward and backward movement of the arm. In addition, there was evidence of complete paralysis of the radial nerve, with wrist drop and paralysis of extension at the elbow, hand and wrist, paralysis of the thumb muscles and loss of supination. The outstanding atrophy was in the deltoid, although there was some atrophy of the triceps, the posterior axillary muscles and the extensors of the hand. The deltoid, triceps and radial reflexes were absent. Horner's syndrome was not present, but there were some swelling and cyanosis and increased perspiration over the hand. There was no evidence of involvement of the rhomboid muscles or of the supraspinatus or infraspinatus muscle, and there was no weakness of the biceps. The sensory changes, which were in the distribution of the axillary nerve, were minimal, but with lesions of the brachial plexus the sensory loss is always much less than would be expected from the known cutaneous distribution of the nerves involved. The syndrome did not correspond to either the upper or the lower arm type of lesion of the brachial plexus, but showed evidence of involvement only of those muscles which are supplied by the branches of the posterior cord of the brachial plexus.

University Hospital.

ENCEPHALOPATHY FOLLOWING INTRAVENOUS ADMINISTRATION OF ARSENICAL PREPARATIONS

DAVID A. BOYD JR., M.D.

AND

LOUIS NIE, M.D.

INDIANAPOLIS

During the past year 4 patients with encephalopathy following treatment with arsenical preparations were admitted to or seen in consultation by the neurological service of the Indianapolis City Hospital. In 2 cases the disease followed routine intravenous administration of neoarsphenamine and severe involvement of the central nervous system progressed to an early fatal termination. In the other 2 cases the complication occurred during the course of five day massive mapharsen therapy and the clinical picture was also alarming, but the patients quickly recovered, without residual manifestations. The striking difference in the clinical course and termination in these cases led us to review the problem of disturbances of the central nervous system following intravenous administration of arsenical preparations.

ENCEPHALOPATHY FOLLOWING ADMINISTRATION OF ARSPHENAMINE

Since the first report, in 1911, of severe neurologic manifestations following the intravenous administration of arsphenamine, there have been numerous publications concerned with this important, and often fatal, complication. Many facts with regard to the incidence and clinical manifestations have been established by Glaser and associates¹ and Globus and Ginsburg,² but some of the etiologic aspects and pathologic features are less well understood. In 158 cases¹ of involvement of the central nervous system it was found that the mortality rate was 76 per cent, and 1 case of fatal cerebral complication occurred in every 5,398 cases in which this drug was used in treatment. The involvement of the central nervous system most frequently (in 50 per cent) followed the second injection of the arsphenamine preparation, although cases were reported in which it followed the fifteenth dose. The neurologic disturbance occurred in either sex at any age; instances of the disorder have been reported in infants of 5 months³ and in adults past 60 years of age. Severe involvement followed small doses, as well as large ones, and occurred after the use of arsphenamine, neoarsphenamine, sulfarsphenamine and sodium arsphenamine. That the syndrome was not due to an accidental

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From the Department of Neurology and Psychiatry, Indiana University School of Medicine and the Indianapolis City Hospital.

1. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamine, *Am. J. M. Sc.* **189**:64, 1935.

2. Globus, J., and Ginsburg, S.: Pericapillary Encephalorrhagia Due to Arsphenamine, *Arch. Neurol. & Psychiat.* **30**:1226-1247 (Dec.) 1933.

3. Black, W. C.: Death from Hemorrhagic Encephalitis Following Treatment with Sulpharsphenamine, *Am. J. Dis. Child.* **51**:609-613 (March) 1936.

toxic quality of the arsenical preparation was shown in 1 case⁴ in which an ampule was divided between 2 patients, 1 of whom had toxic cerebral manifestations and the other did not. At first the symptoms referable to the central nervous system were attributed to an unusually severe Herxheimer reaction, with tissue poisoning from the liberated endotoxins of destroyed spirochetes. However, in the intervening years so many typical cases of the disorder have been reported in nonsyphilitic patients that syphilis is no longer believed to have any important etiologic role.

The clinical features are also well known. The severe manifestations may develop within twelve to one hundred and forty-four hours after the administration of the drug, but the usual time of onset is two and a half days after the injection. The initial symptom is usually intense headache, occurring a few hours after the injection and lasting one or two days, followed by vomiting, convulsions, mental disturbances and stupor. Numerous focal neurologic manifestations have been reported, and these vary widely. Globus and Ginsburg² attempted to define a clinical symptom complex which was characteristic, but found little beyond an array of signs and symptoms which could be caused by any widespread inflammatory or degenerative disease of the central nervous system.

Postmortem examination in cases of this syndrome revealed marked edema and congestion of the brain and multiple petechial hemorrhages, which coalesced to form large hemorrhagic areas throughout the white matter of the cerebrum, cerebellum, midbrain and pons. Because of these conspicuous hemorrhages the syndrome was named "hemorrhagic encephalitis" or "brain purpura." Microscopic examination disclosed that the large hemorrhagic areas were made up of many small foci, which consisted of a dense ring of red blood cells, a clear, unstained center and a central capillary. These ring hemorrhages were considered the pathologic characteristic of arsphenamine encephalopathy. The reason for the ring form of the hemorrhage was uncertain; some authors expressed the belief that the blood came from capillaries surrounding the central precapillary, while others said that the ring form was due to perivascular bleeding, the hemorrhage being subsequently carried outward to form a ring by the swelling of the tissue.

Spielmeyer noted the similarity of these foci to those observed with malaria, pernicious anemia, burns and scarlet fever and called attention to the zone of perivascular necrosis about the central vessel and the wreath of neuroglia interposed between this zone and the outer ring hemorrhage. Alpers⁵ studied so-called hemorrhagic encephalitis in various disorders and expressed agreement with Spielmeyer concerning the perivascular necrosis; he concluded that the hemorrhage was an unimportant feature. Both authors observed foci in which no hemorrhage had occurred and concluded that the perivascular necrosis was the outstanding feature, and Alpers suggested the name "medullary perivascular necrosis" for the condition. However, in none of his cases did this reaction follow the intravenous administration of arsphenamine.

Although the hemorrhagic lesion was usually considered the typical patho-anatomic change associated with arsphenamine poisoning, occasional cases were reported in which hemorrhage was insignificant or absent. Russell⁶ studied a

4. Miller, M.: Four Types of Encephalitis, *J. A. M. A.* **97**:161-164 (July 18) 1931.

5. Alpers, B. J.: So-Called "Brain Purpura" or "Hemorrhagic Encephalitis," *Arch. Neurol. & Psychiat.* **20**:497-523 (Sept.) 1928.

6. Russell, D. S.: Changes in the Central Nervous System Following Arsphenamine Medication, *J. Path. & Bact.* **45**:357-366, 1937.

case in which only a few petechiae were noted, but there were numerous areas of perivascular nonhemorrhagic necrosis. She reported 2 other cases in which both hemorrhagic lesions and perivascular necroses were present and concluded that the nonhemorrhagic type was a less intense tissue reaction. More recently, Roseman and Aring⁷ reported a case in which the changes were identical with those in Russell's first case.

The cause of such neuropathologic lesions is undetermined, although there are numerous theories regarding their origin. Practically all observers have agreed that disturbance of the cerebral vascular system and blood supply is of primary importance, but just how this occurs remains a matter of conjecture. The earlier authors advanced various explanations, such as stasis of blood due to venous thromboses, diapedesis of red blood cells following injury of capillary endothelium or fat embolism with necrosis of capillary walls. Ehrlich⁸ expressed the belief that delayed excretion of arsphenamine due to impaired renal function allows the formation of a derivative (paraminophenylarsenoxide), which has an irritative effect on the capillaries. More recently the hypothesis has been advanced⁹ that the lesions are due to a direct and selective effect of the arsphenamine molecule, or some of its fractions, which has a dilating and destructive action on the vascular endothelium, resulting in congestion, stasis and hemorrhage.

REPORT OF CASES

CASE 1.—A Negress aged 33 was admitted to the hospital on Aug. 25, 1941. Three weeks previously it was discovered that she had syphilis and mild pellagra. Intravenous injections of neoarsphenamine (0.3 Gm.) were instituted; shortly after the second treatment, on August 20, she complained of a severe headache, which continued until August 24. At this time she became unconscious, and she was brought to the hospital the next day.

The patient was in deep coma, and there was marked diaphoresis. The pupils were equal and reacted to light; further neurologic examination gave normal results except for the absence of knee and ankle jerks. The temperature was 97.4 F., and the blood pressure was 130 systolic and 80 diastolic. Urinalysis revealed that the reaction for albumin was 2 plus and that for acetone 2 plus. The blood sugar was 122 mg. and the nonprotein nitrogen 27 mg. per hundred cubic centimeters. The Kline and Kahn reactions of the blood were 4 plus. Examination of the spinal fluid revealed a 1 plus reaction for globulin, no cells, a negative Wassermann reaction, 94 mg. of sugar per hundred cubic centimeters and a Lange curve of 5555543322.

During the next day the patient remained in coma and assumed a position with stiffness of the extremities, suggesting decerebrate rigidity. The right eye deviated laterally, there was slight swelling of the optic disks, and the retinal veins were full. She had numerous generalized convulsive seizures, which began with twitching of the right arm. The tendon reflexes were present in the right upper extremity but were absent in the left. The knee jerks were present and hyperactive; the ankle jerks were absent. The Babinski sign was suggestively positive on the left side.

During the ensuing days the patient continued to have repeated convulsive seizures. She received injections of 50 per cent sucrose, of physiologic solution of sodium chloride and 5 per cent dextrose, as well as epinephrine, but she did not respond and died on August 29.

General Pathologic Examination.—Petechial hemorrhages were observed beneath the endocardium of the right auricle. Except for congestion of the lungs, liver and kidneys and pulmonary edema, further examination revealed nothing remarkable.

7. Roseman, E., and Aring, C. D.: Encephalopathy Following Neoarsphenamine Treatment, *New England J. Med.* **224**:550-553, 1941.

8. Ehrlich, P.: Deaths After Salvarsan: Encephalitis Hemorrhagica, *Brit. M. J.* **1**:1044-1045, 1914.

9. Scott, E., and Moore, R. A.: Fatalities Following the Use of Arsphenamine, *J. Lab. & Clin. Med.* **13**:345-353, 1928; Fatalities Following the Use of Arsphenamine, *Am. J. Syph., Gonorr. & Ven. Dis.* **12**:252-262, 1928. Globus and Ginsburg.²

Examination of the Brain.—The surface vessels of the brain were congested, and the convolutions were swollen and flattened. There was a yellowish discoloration of the superior surface of the corpus callosum. Section of the brain revealed large hemorrhagic areas, formed by the confluence of many small petechiae. They were especially large and abundant in the white matter around the ventricles and in the corpus callosum and the centrum semiovale (fig. 1). The blood vessels throughout the brain were prominent and congested, and many of the smaller ones had a red areola of perivascular bleeding. In the midbrain (fig. 2) were hemorrhagic areas measuring 1 cm. in diameter and similar smaller foci were observed in the pons.



Fig. 1 (case 1).—Large hemorrhagic areas in the white matter due to the confluence of small petechiae.

Microscopic examination of the meninges disclosed pronounced congestion, but nothing else noteworthy. Sections from various parts of the brain revealed generalized edema and congestion. In the cortex there were toxic changes with acute swelling of ganglion cells, but the most outstanding manifestations were in the white matter. The hematoxylin and eosin stain revealed two types of lesions. The lesions with hemorrhage were the most conspicuous and usually consisted of closely packed red blood cells, which overflowed the tissue between the dilated, congested vessels (fig. 3), but hemorrhages of the ring type were also present. The intima of smaller vessels showed swelling and proliferation. Another type of lesion, noted in areas not obscured by hemorrhage, was the nonhemorrhagic area of necrosis, usually

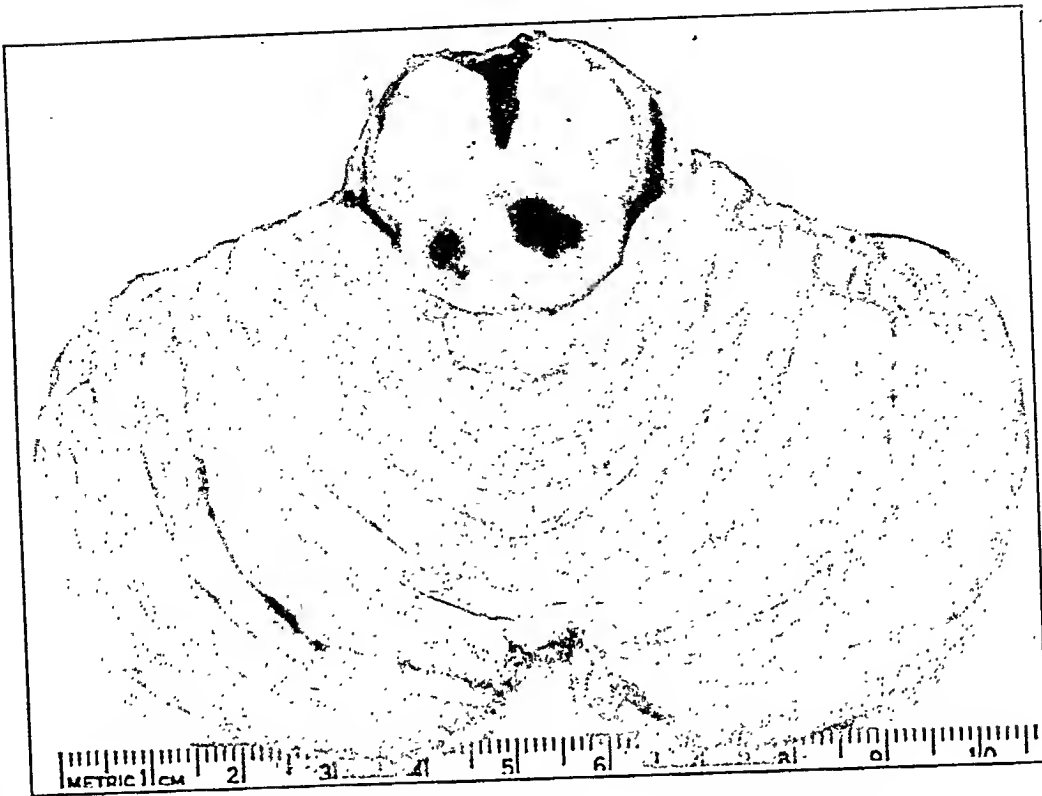


Fig. 2 (case 1).—Hemorrhagic areas in the midbrain.



Fig. 3 (case 1).—Hemorrhage from a dilated and congested capillary into the surrounding white matter. Hematoxylin and eosin stain; $\times 600$.

adjoining a precapillary which contained a hyaline thrombus (fig. 4). Such lesions were spongy in texture and relatively acellular and showed little evidence of a peripheral neuroglial reaction. Occasional ameboid glia cells were noted in these foci. These nonhemorrhagic necroses sometimes occurred singly, but more usually they were in groups, which coalesced to form large necrotic foci. Scarlet red preparations showed no fat in the few cells in these zones.

Spielmeyer preparations revealed focal demyelination surrounding many of the smaller blood vessels (fig. 5). This demyelination occurred in both the hemorrhagic and the nonhemorrhagic foci. Demyelinated zones of equal size might or might not contain blood. No transitional stages between the two types could be seen, and it was impossible to determine whether one type of lesion progressed to the other.



Fig. 4 (case 1).—Nonhemorrhagic area of necrosis adjoining a thrombosed capillary. Hematoxylin and eosin stain; $\times 95$.

CASE 2.—A Negress aged 27 was admitted to the hospital on April 27, 1942 because of convulsions and coma. The only history available was the statement that convulsive seizures followed by coma had begun some thirty hours previously. She had frequent tonic and clonic convulsions and remained in deep coma between seizures. The axillary temperature was 100 F., and there was pronounced diaphoresis. There was marked rigidity of the neck. The arms were held stiffly at the sides, and the legs were maintained rigidly in extension. The pupils were equal and reacted promptly to light. The optic disks were not elevated, and no pathologic condition was noted in the fundi. The tendon reflexes were all present, hyperactive and equal bilaterally. No pathologic reflexes were elicited.

Lumbar puncture disclosed that the cerebrospinal fluid was apparently under increased pressure, but the manometric readings were inaccurate because of faulty connections. Exami-

nation of the spinal fluid revealed a total protein of 278 mg. per hundred cubic centimeters, a 4 plus reaction for globulin, 1 lymphocyte per cubic millimeter, a negative Wassermann reaction, a Lange curve of 0000000000 and a sugar content of 81 mg. per hundred cubic centimeters. The blood count showed 110 per cent hemoglobin, 5,960,000 red cells and 3,750 white cells per cubic millimeter and a normal differential count. Urinalysis revealed a 2 plus reaction for albumin and occasional granular casts. The blood sugar was 115 mg. per hundred cubic centimeters, and the nonprotein nitrogen was 88 mg.

During the next two days the patient remained unconscious and did not respond to treatment. She died on April 30, the temperature rising to 107 F. shortly before death. On this day it was learned that she had received two injections of 0.45 Gm. of neoarsphenamine, the first injection having been administered two weeks and the second dose about one week before her admission to the hospital.

General Pathologic Examination.—Petechial hemorrhages were noted beneath the endocardium, in the myocardium and beneath the mucosa in the pelves of the kidneys. Microscopic

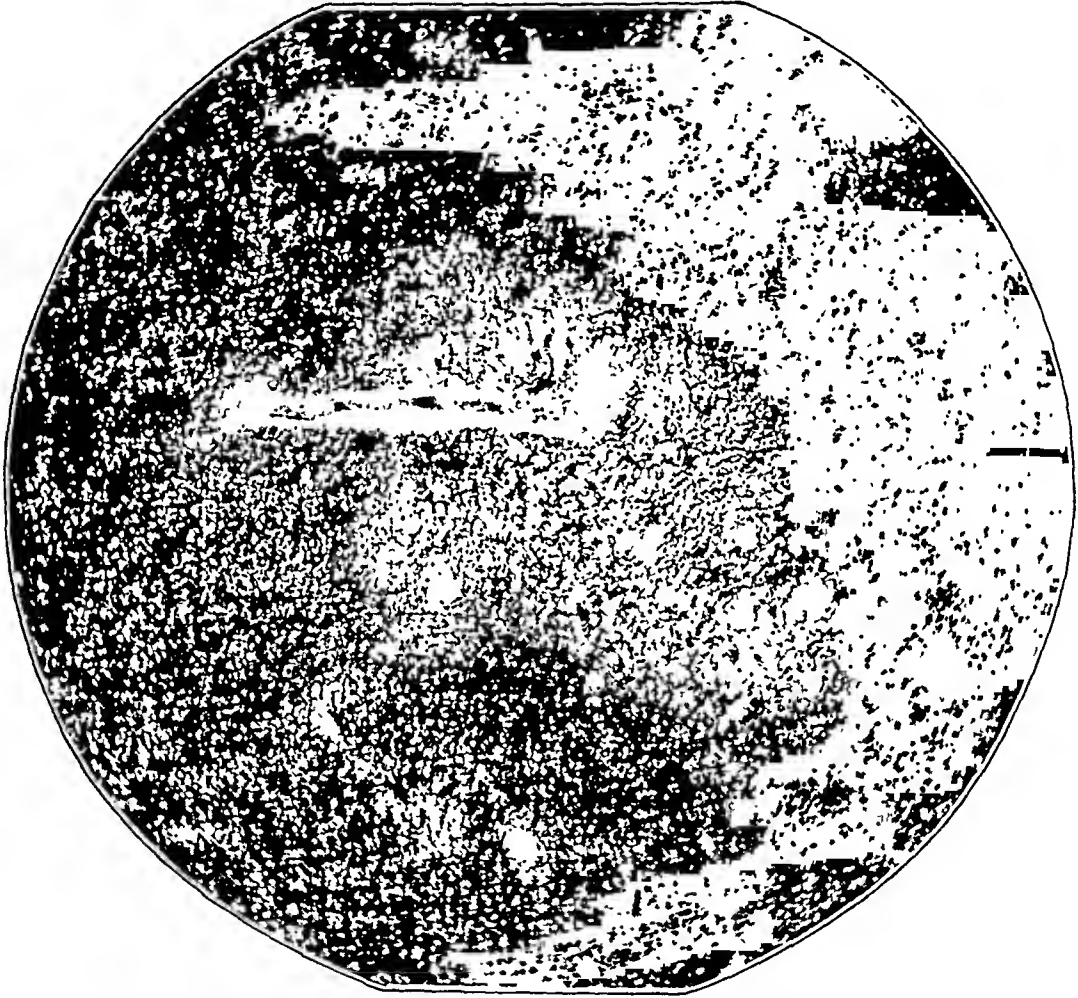


Fig. 5 (case 1).—Focal demyelination about a capillary. Spielmeier stain; $\times 47$.

examination revealed severe degenerative changes in the renal tubular epithelium. Aside from bronchopneumonia and chronic pelvic inflammatory disease, the observations were not remarkable.

Examination of the Brain.—The meningeal vessels were conspicuously congested; the brain was swollen, and the convolutions were flattened. Section of the brain revealed numerous petechial hemorrhages, which were either scattered or fused together to form large hemorrhagic areas. They were especially abundant in the corpus callosum, the internal capsule and the white matter around the lateral ventricles. Large hemorrhagic areas were present in the occipital lobes adjacent to the ventricle. Occasional hemorrhages were observed in the caudate nuclei. Numerous discrete hemorrhages were noted in the midbrain, the superior cerebellar peduncles and the white matter of the cerebellum.

Microscopic examination revealed pronounced congestion and edema throughout the brain. The ganglion cells of the cortex exhibited moderate toxic changes, but no outspoken lesions appeared. Sections from the white matter revealed numerous isolated or fused lesions around

the dilated and congested vessels. Some of these were perivascular hemorrhages, occasionally in ring form (figs. 6 and 7), while others were nonhemorrhagic necroses. In the latter areas were fragments of myelin, but the scarlet red stain did not reveal any fat. No significant glial reaction was observed, although degenerating neuroglia cells were seen in these foci. Spielmeyer preparations (fig. 8) revealed multiple foci of demyelination adjoining small vessels; these foci were either scattered throughout the white matter or fused together to form a large demyelinated area. Some of these perivascular foci were filled with blood, while others of equal size were nonhemorrhagic. In some a small wreath of red blood cells surrounded the central capillary, but the demyelination extended for a considerable distance beyond this thin perivascular hemorrhage.

In both cases the cerebral lesions had a similar distribution in the white matter about the ventricles and in the connecting pathways. The constant proximity to the blood vessels of the nonhemorrhagic necroses and the hemorrhagic lesions



Fig. 6 (case 2).—Global pericapillary hemorrhage. Azan stain; $\times 80$.

was evidence that they both resulted from some initial vascular disturbance. In favorably cut sections it was apparent that the focal nonhemorrhagic necroses adjoined a vessel in which there was marked interference with the flow of blood, due either to stasis or to thrombosis. In structure they resembled lesions described by Putnam and Alexander¹⁰ and others as due to venous stasis and thrombosis, and it is probable that they were focal necroses resulting from vascular disturbance. The hemorrhagic lesions indicated a more severe degree of capillary damage. In case 2 some demyelinated areas contained a few scattered red blood cells or a small ring of blood around the dilated vessel, the hemorrhage into the necrotic foci suggesting that it had occurred as an end result of severe capillary dilatation

10. Putnam, T., and Alexander, L.: Tissue Damage Resulting from Disease of Cerebral Blood Vessels, *A. Research Nerv. & Ment. Dis., Proc.* (1937) **18**:544-567, 1938.

and stasis. Such observations would indicate that the two varieties of lesions, although differing in type, have a common vascular basis and represent differences in degree of tissue injury. The relationship of the various pathologic changes might be explained by the following hypothesis. In some patients pronounced capillary dilatation, stasis and possibly thrombosis occur in the central nervous system after intravenous administration of arsphenamines. Serous exudation from the engorged vessels and edema occur and focal tissue necrosis, owing to pressure and interference with the blood supply, follows. As an end result of the most severe form of capillary injury, hemorrhage into the perivascular foci may occur. Such an explanation of the varying degrees of severity of tissue injury would account

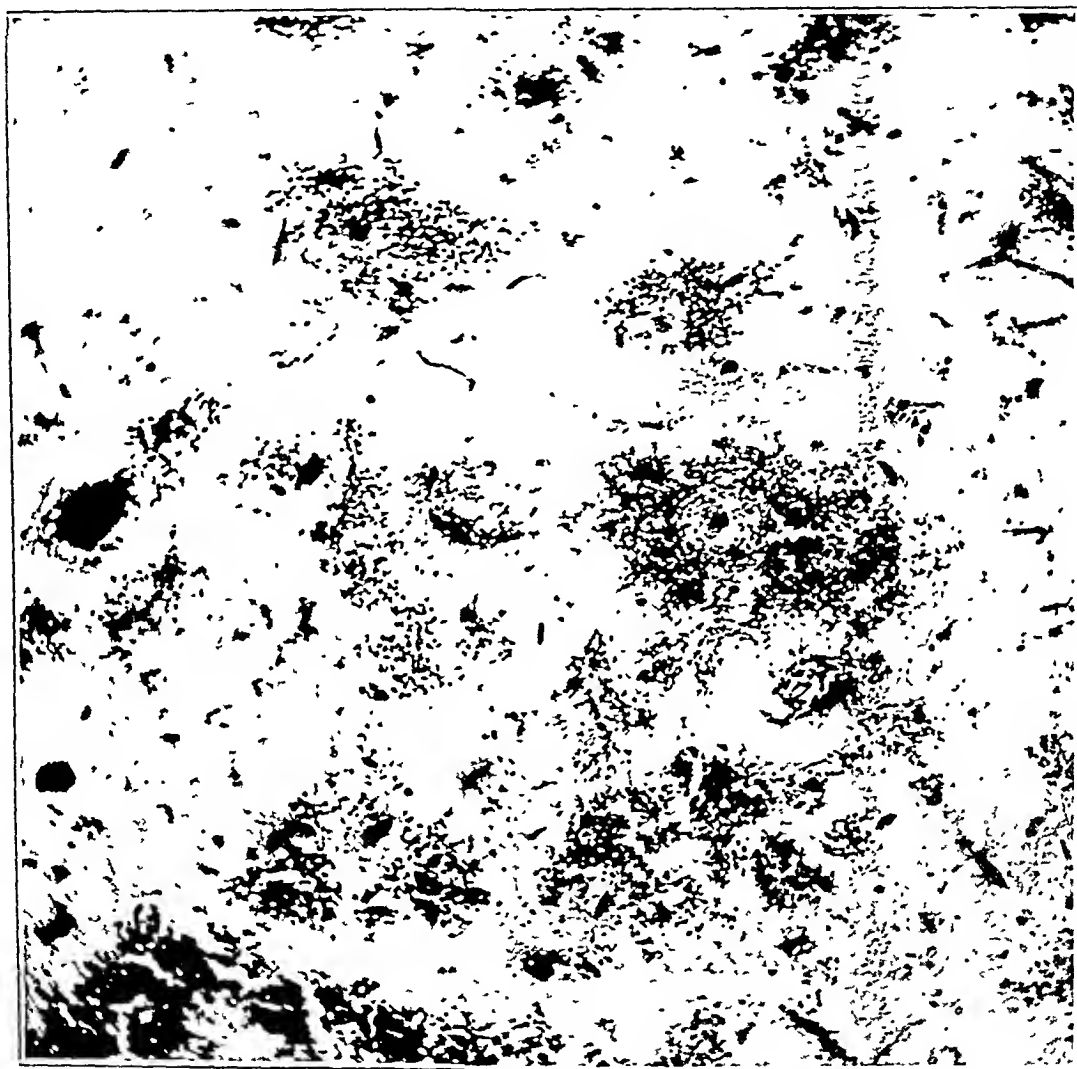


Fig. 7 (case 2).—"Ring hemorrhages" immediately adjoining those shown in figure 6. Azan stain; $\times 80$.

for the differences in the pathologic picture in various cases in the literature. Thus, it is reasonable that in some fatal cases only cerebral congestion and edema, and in others edema and focal demyelination, are present, while in the remainder hemorrhagic lesions predominate.

ENCEPHALOPATHY FOLLOWING FIVE DAY MASSIVE THERAPY WITH MAPHARSEN

The original five day therapy program of Chargin, Leifer and Hyman consisted of daily intravenous infusions of solutions of neoarsphenamine. This preparation was later abandoned because of the occurrence of complications, which included

peripheral neuritis, in 35 per cent of cases, and death due to acute cerebral involvement, in 1 case. Mapharsen was then employed because of its lower toxicity, and 1,200 mg. of this drug administered over a period of five days was established as a safe and effective dosage.¹¹ Mapharsen has proved to be less toxic than neoarsphenamine, but serious manifestations referable to the central nervous system occurred in about 1 per cent of patients undergoing massive mapharsen therapy, and the fatality rate from such complications was about 0.3 per cent. In the following cases acute encephalopathy followed massive therapy with mapharsen.

CASE 3.—A white girl aged 17 years was admitted to the hospital in March 1942 for five day. massive therapy with mapharsen. She had the seropositive, secondary stage of syphilis. The past history included attacks of "rheumatism, double pneumonia and mastoid-

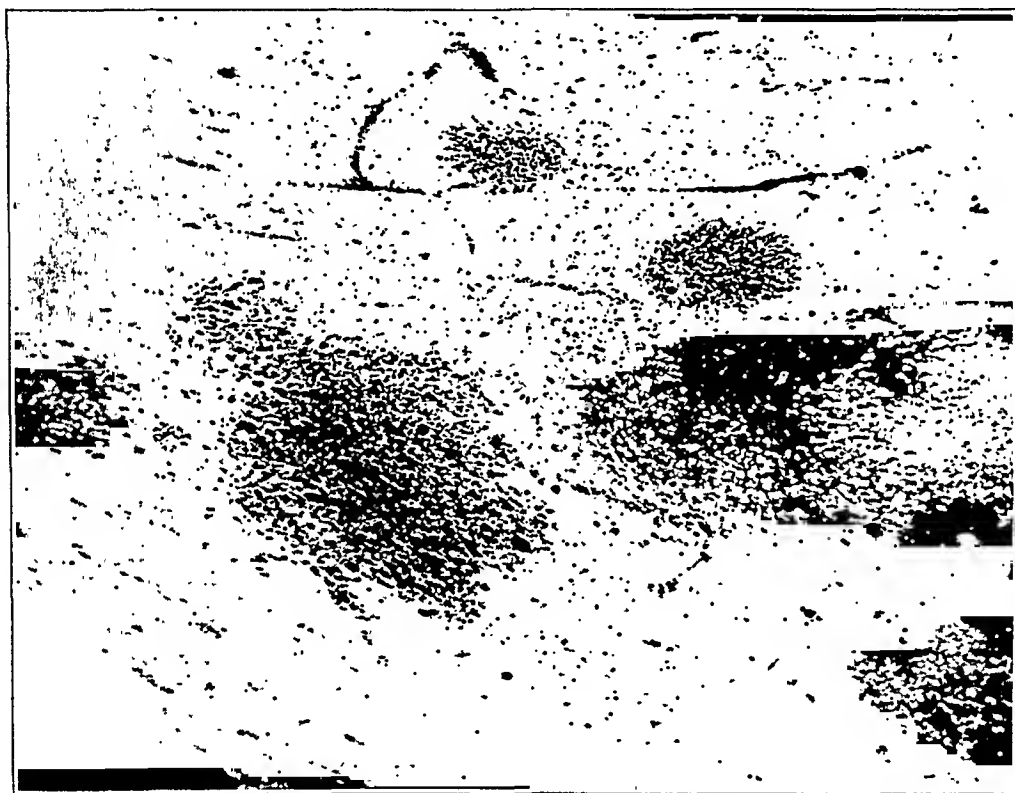


Fig. 8 (case 2).—Foci of demyelination. Spielmeyer stain; $\times 50$

itis" at 8 years of age. In August 1941 she was delivered of a full term child. She was confined to bed during the last two weeks of gestation because of edema of the ankles; at this time she was told she had hypertension and a renal complication. Physical examination

11. Hirshfeld, S.; Hyman, H. T., and Wanger, J. J.: Influence of Velocity on Response to Intravenous Injections, *Arch. Int. Med.* **47**:259-287 (Feb.) 1931. Chargin, L.; Leifer, W., and Hyman, H. T.: Studies of Velocity and Response to Intravenous Injections: Application of Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in Treatment of Early Syphilis, *J. A. M. A.* **104**:878-883 (March 16) 1935; Massive Dose Arsenotherapy of Syphilis by Intravenous Drip Method: Five Year Observations, *Am. J. M. Sc.* **197**:480, 1939. Baehr, G.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method: The Preliminary Work with Neoarsphenamine, *Arch. Dermat. & Syph.* **42**:239-244 (Aug.) 1940. Leifer, W.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, *ibid.* **42**:245-247 (Aug.) 1940. Rice, J. L.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, *ibid.* **42**:283-284 (Aug.) 1940. Hyman, Chargin, Rice and Leifer.^{14a} Chargin.^{14b} Elliott and others.¹⁷ Leifer, Chargin and Hyman.²¹

gave normal results except for the cutaneous lesions. Hemocytologic examination revealed 80 per cent hemoglobin, 4,360,000 red cells and 6,300 white cells per cubic millimeter and a normal differential count. The nonprotein nitrogen of the blood measured 29 mg. per hundred cubic centimeters. Urinalysis revealed a faint trace of albumin.

On the first day of treatment there were nausea, vomiting and accentuation of the secondary lesions. During the second day the patient complained of aching and weakness of the lower extremities; this was worse on the third day, and the nausea and vomiting were more severe. On the fourth day she was given thio-bismol, 0.2 Gm. intramuscularly, in addition to the regular infusion of mapharsen. Nausea, vomiting and weakness and pain in the legs continued throughout the fifth day, but she completed the course of treatments, receiving 1,200 mg. of mapharsen, in daily doses of 240 mg.

During the morning of the sixth day (first post-therapy day) she became apprehensive and confused and complained of pounding headache and stiffness and aching of the legs. Neurologic examination gave essentially normal results. Lumbar puncture revealed a pressure of 260 mm. of water, and examination of the fluid disclosed a 1 plus reaction for globulin, a total protein content of 95 mg. per hundred cubic centimeters, 4 lymphocytes per cubic millimeter, a 4 plus Wassermann reaction, 58 mg. of sugar per hundred cubic centimeters and a Lange curve of 1123311000. Urinalysis revealed a trace of albumin and a 4 plus reaction for urobilinogen. The nonprotein nitrogen of the blood was 22 mg. per hundred cubic centimeters.

On the seventh day the patient continued to be lethargic and confused and complained of photophobia and generalized pain. Lumbar puncture revealed a pressure of 160 mm. of water, and examination of the fluid disclosed a 1 plus reaction for globulin, 11 lymphocytes and 3 red blood cells per cubic millimeter, a 4 plus Wassermann reaction, a total protein content of 263 mg. per hundred cubic centimeters and a Lange curve of 4444333310. During the eighth day she was semistuporous and delirious and screamed when the extremities were touched or moved. There was puffiness about the eyes, and a toxicoderma was distributed over the entire body. Neurologic examination revealed irregularity of the right pupil, which was larger than the left, but both pupils reacted to light. Extraocular movements were normal, and there was no nystagmus. The retinal veins were distended, and the outline of the disks was blurred, with slight elevation of the left. Examination of the rest of the cranial nerves revealed nothing abnormal except for slight weakness of the left side of the face and marked tremor of the tongue. The deep reflexes of the arms were hyperactive but bilaterally equal. The knee and ankle jerks were normal and equal on the two sides. Abdominal reflexes were absent. The Kernig and Brudzinski signs were positive. No pathologic reflexes were elicited. There was pronounced tenderness to pressure over the nerve trunks and muscles. Examination of the spinal fluid revealed a 1 plus reaction for globulin, 8 lymphocytes and 70 red blood cells per cubic millimeter, a 4 plus Wassermann reaction, a total protein of 249 mg. per hundred cubic centimeters and a Lange curve of 0111233210. On the tenth day the pain in the legs was diminished, and mental symptoms had disappeared except for short periods of confusion. The patient was able to move the extremities, and the tremor of the tongue was diminished. Examination of the spinal fluid revealed no cells, a 4 plus Wassermann reaction, a Lange curve of 0001222000 and a total protein content of 142 mg. per hundred cubic centimeters.

On the fifteenth day she regained bladder control, which had been lost on the eighth day. Spinal fluid pressure on the twenty-third day was normal, and the fluid contained a faint trace of globulin, 93 lymphocytes per cubic millimeter, a negative Wassermann reaction, a Lange curve of 0000000000 and 55 mg. of sugar and 47 mg. of total protein per hundred cubic centimeters. When she was discharged, on the twenty-fourth day, she presented no symptoms except slight hyperesthesia and pain on pressure over the nerve trunks. The psychiatric and neurologic examinations gave completely normal results.

The patient gained weight and strength rapidly during the next two months. At this time she felt better than before treatment and had more energy and fewer headaches. There were no residual manifestations of the acute encephalopathy. The spinal fluid pressure was normal, and examination of the fluid revealed no globulin, 3 cells per cubic millimeter, a negative Wassermann reaction, a Lange curve of 0000000000 and a total protein content of 24 mg. per hundred cubic centimeters.

CASE 4.—A white man aged 32 was admitted to the hospital for five day massive treatment with mapharsen. He had the acute secondary stage of syphilis, and dark field and serologic examinations gave positive results. His past history was essentially without significance except for "fainting attacks" when he was frightened. Physical examination revealed nothing abnormal but the cutaneous lesions and pallor. Hemocytologic examination revealed 77 per cent hemoglobin, 4,020,000 red cells and 6,300 white cells per cubic millimeter and a normal differential count. The platelet count was 230,000 per cubic millimeter. Urinalysis gave normal results.

On the first day of treatment, after he had received intravenously 800 cc. of the solution of mapharsen (0.096 Gm.), the patient became dizzy and cyanotic and vomited, and a generalized convulsive seizure followed. After a few moments he felt well, and therapy was continued that day, without untoward manifestations. On the second and third days there were no complaints, and the cutaneous lesion began to fade. The temperature rose each day to 100 F. At the end of the fourth day of therapy he complained of frontal headache and malaise. During the fifth day he complained of such severe venous pain that he received a hypodermic injection of $\frac{1}{4}$ grain (0.011 Gm.) of morphine sulfate. However, he completed the full course of treatments, receiving 1,200 mg. of mapharsen, in five daily doses of 240 mg. In the early evening the patient vomited and appeared apprehensive. Throughout the sixth day (the first post-therapy day) there were marked tremors of the hands and lips and complaints of headache and anxiety. Lumbar puncture disclosed an apparently normal spinal fluid pressure, and examination of the fluid revealed a 3 plus reaction for globulin, 405 red blood cells per cubic millimeter, a negative Wassermann reaction, 103 mg. of sugar per hundred cubic centimeters and a Lange curve of 4433332110. Urinalysis gave normal results except for a faint trace of albumin. During the night of this day and the seventh day he had five severe convulsive seizures, and between the attacks he was restless, irrational and semistuporous. Each convulsion was preceded by a cry, followed by a tonic and clonic phase, with cyanosis and incontinence. Neurologic examination revealed that he was semistuporous and did not respond to verbal commands; he reacted to painful stimuli with an unintelligible mutter and drawing away of the extremity. There was slight rigidity of the neck. The pupils were equal in size and reacted sluggishly to light. The extraocular movements appeared normal. The optic disks were normal. The tendon and abdominal reflexes were absent bilaterally. No pathologic reflexes were elicited. Urinalysis revealed a trace of albumin.

The convulsive seizures were controlled by intravenous injection of sodium amytal. A hypodermic injection of 1 cc. of a 1:1,000 solution of epinephrine hydrochloride was given every four hours, and 1 Gm. of sodium thiosulfate was administered intravenously each day. A 5 per cent solution of dextrose was given by proctoclysis.

During the eighth day the patient was awake and was fairly rational and cooperative; no convulsive seizures had occurred since the preceding afternoon. Lumbar puncture revealed a spinal fluid pressure of 150 mm. of water. On the ninth day the patient was rational and able to eat, and on the next day he was allowed out of bed. Examination of the spinal fluid on the tenth day revealed a 1 plus reaction for globulin, 1 cell per cubic millimeter, a negative Wassermann reaction and a Lange curve of 1112221000. His further course was uneventful, and there have been no psychologic or neurologic manifestations in the ensuing months which suggest that permanent damage had occurred in the central nervous system. His physical condition has been excellent.

Administration of mapharsen, either by the routine interval method or in massive doses, has resulted in fewer complications than occur with neoarsphenamine administered in a similar manner. According to Sobotka and associates,¹² when mapharsen is used in the five day treatment the percentage rate of excretion of arsenic in the urine and feces is higher than when neoarsphenamine is employed. However, in unusual cases in which elimination is deficient, the excretion rate of arsenic during massive mapharsen therapy may approximate that found during treatment with neoarsphenamine. In the usual case of five day mapharsen therapy¹² the arsenic concentration of the blood begins at zero, rises and falls sharply during each day of treatment but gradually increases to a maximum concentration of 1:3,000,000 on the afternoon and evening of the fifth day. A concentration of 1:5,000,000 to 1:3,000,000 is maintained during the fourth, the fifth and most of the sixth day.¹³ This observation may be of significance in view of the fact that in 2 cases in the literature¹⁴ the acute cerebral symptoms began on the seventh day (after massive neoarsphenamine and massive mapharsen therapy respectively)

12. Sobotka, H.; Mann, W., and Feldbau, E.: Massive Arsenotherapy in Early Syphilis by the Intravenous Drip Method, *Arch. Dermat. & Syph.* **42**:270-276 (Aug.) 1940.

13. Hyman, H.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, *Arch. Dermat. & Syph.* **42**:253-261 (Aug.) 1940.

14. (a) Hyman, H. T.; Chargin, L.; Rice, J., and Leifer, W.: Massive Dose Chemotherapy of Early Syphilis by the Intravenous Drip Method, *J. A. M. A.* **113**:1208-1212 (Sept. 23) 1939. (b) Chargin, L.: Massive Arsenotherapy in Early Syphilis by the Continuous Intravenous Drip Method, *Arch. Dermat. & Syph.* **42**:248-252 (Aug.) 1940.

and that in our cases the signs of serious involvement of the central nervous system appeared in the morning and the evening respectively of the sixth day. This suggests the possibility that the acute manifestations in these cases occurred shortly after the maximum concentration of arsenic in the blood had been reached.

The question arises whether the cerebral complications following massive administration of mapharsen were identical with those following massive treatment with neoarsphenamine. One gains the impression from various observers that the cerebral syndrome following treatment with mapharsen is not as fatal as that following treatment with neoarsphenamine. A comparison of the pathologic pictures in the two conditions establishes their relationship, but the available data concerning the cerebral pathologic changes after therapeutic doses of mapharsen is too meager to warrant definite conclusions. In a recent review of the literature since 1935, Levin and Keddie¹⁵ found only 1 fatality from "hemorrhagic encephalitis" due to routine administration of mapharsen. The clinical manifestations in this case, as reported by Rajam and Rao,¹⁶ were those of an acute encephalopathy, and postmortem examination revealed edema of the brain with congestion of the surface vessels. However, there was no report of the examination of sections of the brain, and it is not known whether lesions were present in the cerebral tissue. Elliott and associates¹⁷ described briefly the lesions in 3 cases of acute encephalopathy following five day treatment with mapharsen in which the clinical course was typical. In the first case there were areas of early focal demyelination but no petechiae or hyaline thrombi; in the second case only cerebral edema was noted, while in the third case the histologic diagnoses were cerebral congestion and edema, with petechial hemorrhages in the nuclei of the twelfth nerves.

In our cases the clinical features conformed to those usually described for arsphenamine encephalopathy except that they were of milder degree and of shorter duration and the patients recovered rapidly, without residual manifestations. Although the clinical signs were alarming, they disappeared in a few days, either through self limitation or in response to therapeutic measures designed to reduce intracranial pressure. In view of the brief clinical course in our cases, the rapid recovery and the meager available data concerning cerebral pathologic changes following five day mapharsen therapy, it is possible that the involvement of the central nervous system differed in degree, if not in kind, from that usually observed after arsphenamine. The pathologic changes in our cases may have been similar to those reported by Elliott and associates¹⁷ and have consisted of intense cerebral congestion and edema without widespread hemorrhagic lesions. Such acute cerebral congestion and edema have been described by Milian¹⁸ as "serous apoplexy," by Phelps and Washburn¹⁹ as "delayed vasomotor reactions" and by Cantarow and Crawford²⁰ as "acute cerebro-meningeal congestion and edema." This type

15. Levin, E., and Keddie, F.: Toxic Effects Following the Use of Mapharsen, *J. A. M. A.* **118**:368-370 (Jan. 31) 1942.

16. Rajam, R. V., and Rao, N. V.: Mapharside in the Treatment of Syphilis, *Indian M. Gaz.* **74**:24-27, 1939.

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19. Phelps, J. R., and Washburn, W. A.: Toxic Effects of Arsenical Compounds Employed in the Treatment of Syphilis in the United States Navy, *Urol. & Cutan. Rev.* **34**:458-476, 1930.

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of cerebral pathologic reaction is possibly less severe than widespread hemorrhagic involvement and, although fatal in some cases, presumably represents a more reversible process. Such an assumption suggests that the patient might be benefited by therapeutic measures to relieve cerebral congestion and edema, and this appeared to be true in our cases. In addition, Leifer and associates²¹ maintained that the most effective treatment of this condition consists of repeated lumbar taps and intravenous injections of dextrose, sucrose and saline solution.

COMMENT

Considerable confusion has existed regarding the cause, nature and relation of the various types of cerebral complications following administration of arsphenamines. Many conflicting ideas have been offered, but the most plausible hypothesis is that suggested by Globus and Ginsburg, i. e., that all the cerebral disturbances are due to a direct effect of arsphenamine, or some of its fractions, on the endothelial lining of the capillaries and that vascular injury is the essential factor in the various reactions. The different types of cerebral syndromes represent quantitative variations of a basically similar process. Thus, the dilatation of capillaries in the nitritoid reaction is but a milder degree of the severe cerebral congestion and edema of "serous apoplexy." Hemorrhagic encephalopathy would represent a more drastic form of damage to the vessels. This hypothesis would explain the clinical and pathoanatomic variations of encephalopathy due to arsphenamines noted in different cases. Thus, in some cases the pathologic changes would be those of congestion, stasis and edema with focal necroses, while in others a predominantly hemorrhagic picture, or varying admixtures of the two processes, would be present.

The concept of Globus and Ginsburg still does not explain why such vascular injury occurs in some patients and not in others. This susceptibility of certain patients has been variously explained as due to individual idiosyncrasy to the drug, sensitization of the capillaries by preceding doses of the medication, lack of epinephrine due to adrenal insufficiency or a toxic concentration of arsenical products in the blood because of deficient elimination of previous doses of the drug. However, none of these theories have been substantiated, nor do they supply an adequate explanation of all the factors in different cases. Individual susceptibility, which may vary at different times, owing to unknown local cerebral or general metabolic conditions, must play a role, as well as factors which enhance a toxic accumulation of arsenical products in the blood. In our cases the occurrence of serious cerebral manifestations at the end of the period of mapharsen therapy suggests that the terminal high concentration of arsenic plays an important role in the appearance of the acute syndrome. It is not inconceivable that deficient elimination of arsenic, due to individual metabolic idiosyncrasy or to disturbance of renal or intestinal function, might cause an abnormally high concentration in the blood in such cases. The greater susceptibility of pregnant women to complications after arsphenamine therapy and the preceding renal disturbance in our case 3 suggest that some renal factor may be the basis of abnormal retention of arsenic.

SUMMARY

Four cases of encephalopathy following intravenous administration of arsenical preparations are reported. In 2 cases, in both of which the disturbance followed the second injection of neoarsphenamine, the syndrome terminated fatally, and

21. Leifer, W.; Chargin, L., and Hyman, H. T.: Massive Dose Arsenotherapy of Early Syphilis by Intravenous Drip Method, *J. A. M. A.* **117**:1154-1160 (Oct. 4) 1941.

pathologic examination revealed vascular congestion and stasis, edema, focal necroses and capillary hemorrhages throughout the cerebral white matter, a picture suggesting that stages or degrees of tissue injury occurred. The lesser degrees of involvement, which include congestion, edema, focal necroses and demyelination, may eventuate fatally,²² but theoretically they represent a more reversible type of reaction. The capillary hemorrhages are the final or most severe type of injury, and a favorable outcome is less likely after extensive bleeding has occurred. According to this assumption, the clinical syndrome of arsenical encephalopathy is a symptomatic expression of a series of cerebral changes, graduated in severity, which stem from an initial vascular disturbance. Therefore, capillary hemorrhage, instead of representing a pathologic hallmark of the disorder, merely indicates the degree and severity of the process.

In the 2 cases of encephalopathy following massive mapharsen therapy it is only possible to surmise the nature of the cerebral pathologic reaction. That the process may have been one of capillary stasis and congestion with cerebral edema is suggested by its short course and rapid reversal. Such a hypothesis not only is in harmony with the observed lower mortality rate of mapharsen encephalopathy and the meager pathologic data now available but suggests that the treatment of choice is some measure which would reduce cerebral edema. Finally, the chronologic concurrence of the onset of signs of encephalopathy and the maximum sustained levels of arsenic in the blood, as shown by estimations in other cases of massive arsenical therapy, is probably not fortuitous. The possibility of such a relation between the capillary disturbance and high levels of arsenic in the blood indicates a need for further information concerning the factors which impede the elimination of arsenic and promote its accumulation in the blood.

Indiana University School of Medicine.

Indianapolis City Hospital.

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RETROGRADE DEGENERATION

EFFECT OF HEMISECTIONS ON THE HOMOLATERAL AXONS OF THE SPINAL CORD

A. M. LASSEK, M.D., PH.D.

CHARLESTON, S. C.

Neuron regeneration in all parts of the nervous system has always been of great theoretic and practical interest. Currently, the war has acted as a stimulus to additional investigative work on this general subject. While functional and anatomic regeneration following transection has been reported to occur in the spinal cord of the rat,¹ it apparently has never been conclusively shown in other animals that the part of the axon attached to the cell body is structurally maintained when the neuron is severed. On the basis of studies made on nerve cells by Nissl's method of retrograde degeneration, one would expect regeneration of central neurons to be impossible, since it is for the most part believed that the central neuron is dependent on all of its morphologic parts for its survival. Loss of such a small portion as the telodendron of the optic nerve fiber, for example, is supposed to cause dissolution of the entire neuron.² In a recent investigation, I was unable to find any loss of fibers in the pyramids in the monkey ten months after severing the pyramidal fibers at the level of the first cervical segment, although the Betz, or giant, cells of the motor cortex did show pronounced changes.³ Because the results of these axonal studies were contrary to the majority of interpretations made in studies of retrograde cellular changes, it was decided to investigate the subject further by noting the effects produced on the homolateral axis-cylinders after hemisections in various parts of the spinal cord of the cat and the monkey.

MATERIAL AND METHODS

Hemisection of the spinal cord was made on the left side in 6 adult cats at the following levels: first cervical (3 cats) and second thoracic, fifth thoracic and third lumbar (1 each). In 1 monkey a hemisection was performed at the first thoracic level. The cats with lesions at the first cervical level were killed one, three and ten months after operation; all the others, including the monkey, were allowed to survive ten months. During the course of the investigations, practically all of the standard neurologic stains, including the Marchi method, were applied to various sections above and below the lesions. In the case of the cat which was kept ten months after operation, cresyl violet was utilized to stain sections through area 4; these sections were taken 500 microns apart.⁴

RESULTS

All the animals, before they were killed showed characteristic physiologic defects. The hemisections appeared to be complete on gross and microscopic examination. In most instances the section extended slightly beyond the midregion

From the Department of Anatomy, Medical College of the State of South Carolina.

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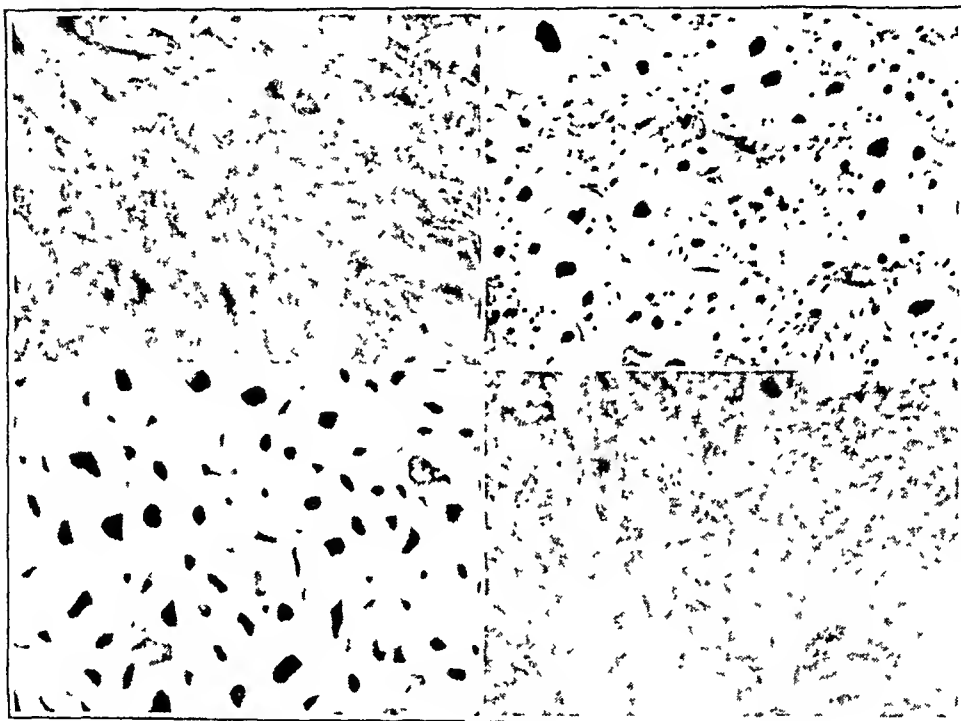
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4. Miss Margaret Powers, technician, handled all phases of the staining procedure.

of the cord, either posteriorly or anteriorly. Histologically, the axons within the spinal cord of the cat and monkey seem to be resistant to retrograde breakdown and disappearance. If a lesion is made in any of the regions mentioned, the motor fibers in the segment above and the sensory fibers in the segment below the injury do not undergo disintegration in ten months, nor is gliosis in evidence. In these experimental animals, no overt changes in the axons were noted in the pyramids.

Area 4 (motor cortex) was studied in the cat which had survived ten months with a hemisection at the first cervical segment. The sections were difficult to evaluate because it appeared at first hand that the so-called giant, or Betz, cells had disappeared. However, if that were true, it would seem that some of the fiber components should be missing in the pyramid below. It may be that these cellular elements undergo such mutations that any resemblance to a normal cell is lost. They may remain in a state whereby they can maintain the anatomic integrity of the axons.



Untouched photomicrographs of silver-stained sections of the spinal cord of the cat taken at the first and ninth thoracic segments ten months after a hemisection at the fifth thoracic level. On the left side are sections of the fasciculus gracilis above and below the lesion; on the right side, sections of pyramidal tract superior and inferior to the injury. Magnification $\times 720$.

One of the noticeable characteristics of the investigation was the remarkable repair which occurred within ten months after damage to the cord. Of the silver stains employed, Ranson's silver-pyridine method seems to have more predilection for staining the glial tissue than does the protargol (strong protein silver) method; thus, it is more suitable for the following of older degenerated pathways.

COMMENT

Nissl's method of retrograde degeneration has been employed by many investigators during the past fifty years in studying the origin of fiber systems. Their efforts apparently have been primarily concentrated on changes in the cellular elements rather than on the entire neuron. In the central nervous system, one

of the consistent changes reported after section of an axon has been partial or complete disappearance of the nerve cells constituting the cells of origin. Holmes and May⁵ observed that about one fourth or more of the so-called Betz, or giant, cells of the motor cortex in the dog had disappeared twenty-three days after a hemisection at the first cervical level; approximately the same phenomenon occurred as early as twenty-eight days in the cat and forty-nine days in the monkey. Levin and Bradford⁶ reported the disappearance of almost all the affected Betz cells twenty-eight days after a hemisection at the cervical fourth segment in the monkey. Polyak² stated that complete loss of cells seems to be the rule in all cases of injury to the neurons within the central nervous system, with the one exception of the dentate nucleus of the cerebellum. On the basis of these cellular interpretations one would have to assume that all ascending and descending fibers would quickly be lost after a transection. Nothing but intersegmental axons should remain intact.

My present results with hemisection of the spinal cord are not in harmony with the view that the cells of origin disappear so quickly, or at all, when the axons of a tract in the cord are sectioned. Motor axons above a lesion in any region of the spinal cord and the sensory axons below the lesion appear to remain intact anatomically at least ten months in the cat and monkey. Tower,⁷ who was not interested primarily in retrograde degeneration, observed fibers in the pyramids of the monkey as long as thirty-two months after damage to the pyramidal tract in the medulla. I believe it was the consensus about the beginning of the twentieth century that breakdown of myelin extended only one or several segments beyond the lesion after damage to the human cord.⁸ If the cells of origin of the fibers severed by hemisection of the cord dissolve and quickly melt away, I believe the neuron theory would not be applicable to the lower portion of the central nervous system. Cells may possibly change to such an extent that evaluation of their presence or absence may be difficult. Such questions as the distance of the injury from the cell body, the presence of collaterals or the maintenance of function in the cut axons have not been considered in this problem. The first two factors may be important in the preservation or dissolution of severed axons; so an investigation has been started in which they can be more easily controlled than in the spinal cord.

In this problem, the region of the lesion was prepared in such a manner that it could not be studied for evidence of nerve regeneration. Since the axons appear to retain their integrity, this phenomenon might potentially be possible.

CONCLUSIONS

Retrograde degeneration, implying breakdown and disappearance of axons, has not been observed to occur in the long motor or sensory tracts of the spinal cord of the cat or monkey within ten months after hemisection.

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CERVICAL SYRINGOMYELIA AND SYRINGOMYELIA-LIKE STATES ASSOCIATED WITH ARNOLD-CHIARI DEFORMITY AND PLATYBASIA

BEN W. LICHTENSTEIN, M.D.

CHICAGO

Compression of the neuraxis at or about the level of the foramen magnum may result in a variety of histopathologic states. In many instances the anatomic picture resembles that of syringomyelia, and in some cases the clinical picture is indistinguishable from that produced by the latter disorder. Platybasia and true syringomyelia may be coexistent pathologic states, and the lack of continued improvement after decompression of the foramen magnum may be due to the primary disease of the spinal cord. From a large source of material, I have chosen cases illustrating a number of conditions seen in the cervical portion of the spinal cord in association with compression of the neuraxis at the foramen magnum.

MATERIAL

The cases in groups 1 and 2 were those of spina bifida complicated by hydrocephalus, and death resulted from sepsis due to pressure necrosis of the tissues overlying the bifida defect, complicated by leptomeningitis. In some instances various stages of a single process were chosen from different cases in an effort to present the complete pathologic picture.

GROUP 1: SYRINGOMYELIA-LIKE STATES ASSOCIATED WITH THE ARNOLD-CHIARI DEFORMITY

A. "ISCHEMIC" LIQUEFACTION NECROSIS

Historical Notes.—In 1894 Arnold¹ described a curious malformation of the hindbrain occurring in a case of spina bifida, and in the following year Chiari² more fully described the deformity in a series of 7 cases of spina bifida. Prior to this time Chiari,³ in 1891, had noted an isolated instance in which the fourth ventricle of the brain extended downward to the fifth cervical vertebral segment. In 1907 Schwalbe and Gredig⁴ gave a detailed description of this deformity and called it the Arnold-Chiari malformation, under which term it has continued to be designated in the literature. I⁵ recently showed that the Arnold-Chiari

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From the Illinois Neuropsychiatric Institute; the Department of Neurology and Neurological Surgery, University of Illinois, and the Cook County Hospital.

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deformity found in association with spina bifida is not a developmental defect but is rather the result of the downward migration of the hindbrain due to fixation of the spinal cord, its meninges and/or its roots at the site of the bifida defect. This downward migration also occurs in instances of platybasia and brevicollis

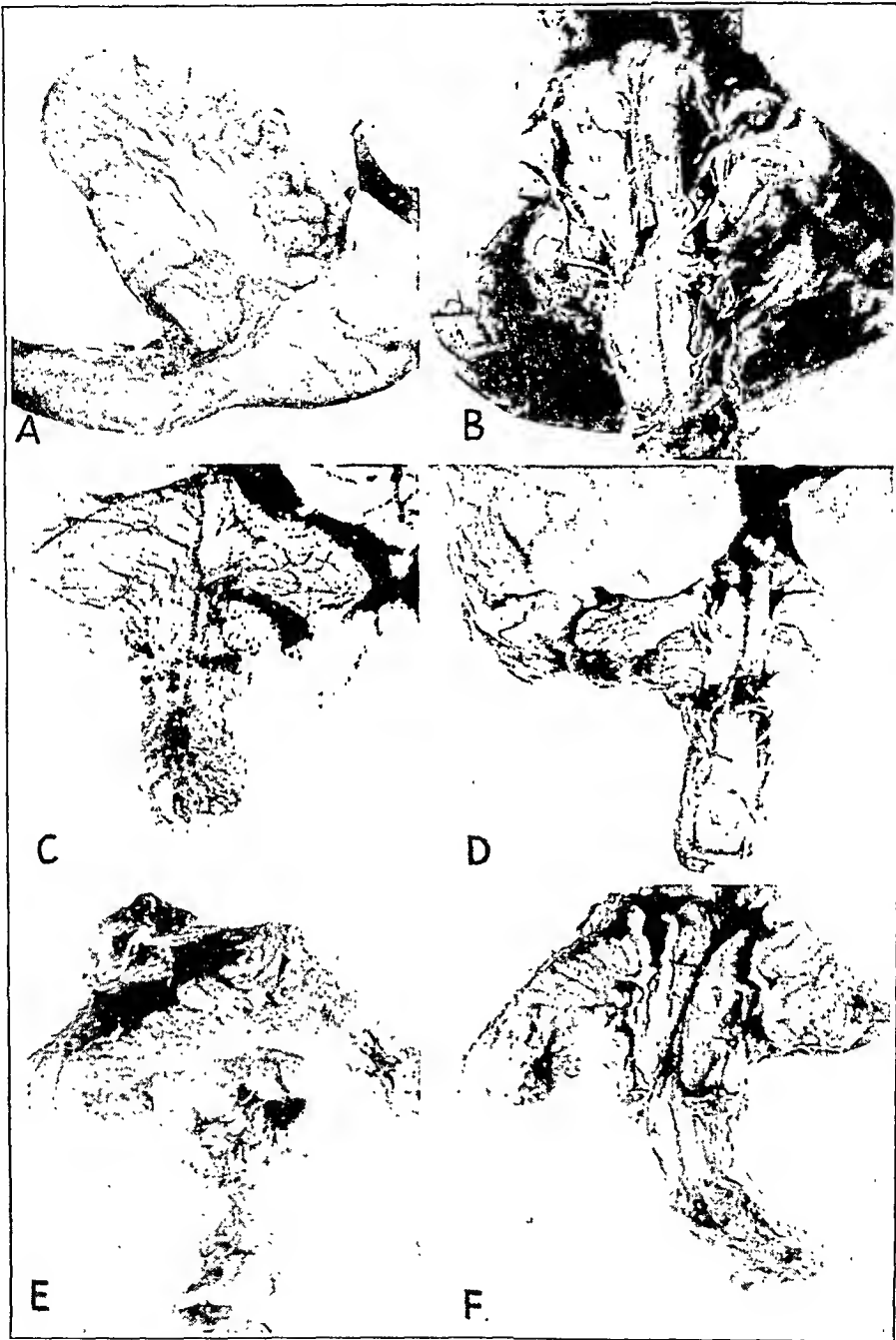


Fig. 1.—Photographs of the hindbrain and upper cervical portion of the spinal cord in cases of spina bifida. The elongation and narrowing of the pons (*B*, *D* and *F*), the deep impression of the basilar artery, the localization of the medulla oblongata below the constriction ring produced by the atlas, the cyanosis of the leptomeninges (*C*) and the intra-medullary cavity (*E*) are striking gross changes.

(Klippel-Feil syndrome), in which the decreased size of the posterior fossa crowds the hindbrain into the upper cervical portion of the spinal canal.

Gross Pathologic Observations.—In almost every instance of hydrocephalus complicating spina bifida the dural sac was observed to be sharply constricted by the arch of the atlas and the rim of the foramen magnum. The site of compression could be clearly seen in all cases after cutting through the bony ring and opening the dura mater (fig. 1). In some specimens the leptomeninges below the constricting bony ring was cyanotic (fig. 1 C).

Microscopic Observations.—Blocks were cut from various portions of the brain and spinal cord and embedded in pyroxylin or paraffin. Sections cut from these blocks were prepared according to a variety of staining methods and impregnation technics, and frozen sections were stained for fat.

A low power photomicrograph taken from a section through the hindbrain cut in a parasagittal plane (fig. 2) shows the constriction of the pontomedullary



Fig. 2.—Very low power photomicrograph of a section taken from the brain stem shown in figure 1 A, showing the localization of the medulla oblongata below the impression produced by the arch of the atlas. Note the venous and capillary stasis and the partial demyelination below the constriction. Here, *oliv* indicates the olivary body; the arrow, the site of the atlas, and *F*, the focus of capillary stasis. Weil stain.

junction at the site of the foramen magnum, the caudal elongation of the pons Varolii and the localization of the medulla oblongata within the spinal canal (the Chiari deformity). The choroid plexus of the fourth ventricle and the posterior medullary velum are similarly compressed at the craniospinal junction. In a higher power photomicrograph taken through the neuraxis just below the constriction and stained by Weil's method (fig. 3 A), one sees areas of incomplete demyelination and extreme engorgement of the capillaries and venules. A high power photomicrograph of a section through the center of the aforementioned affected area stained with toluidine blue (fig. 3 B) shows notably increased cellularity, the cells being chiefly astrocytes and microglial elements. Occasional red blood cells are seen outside the capillaries, and histiocytes filled with granules of blood pigment are everywhere.

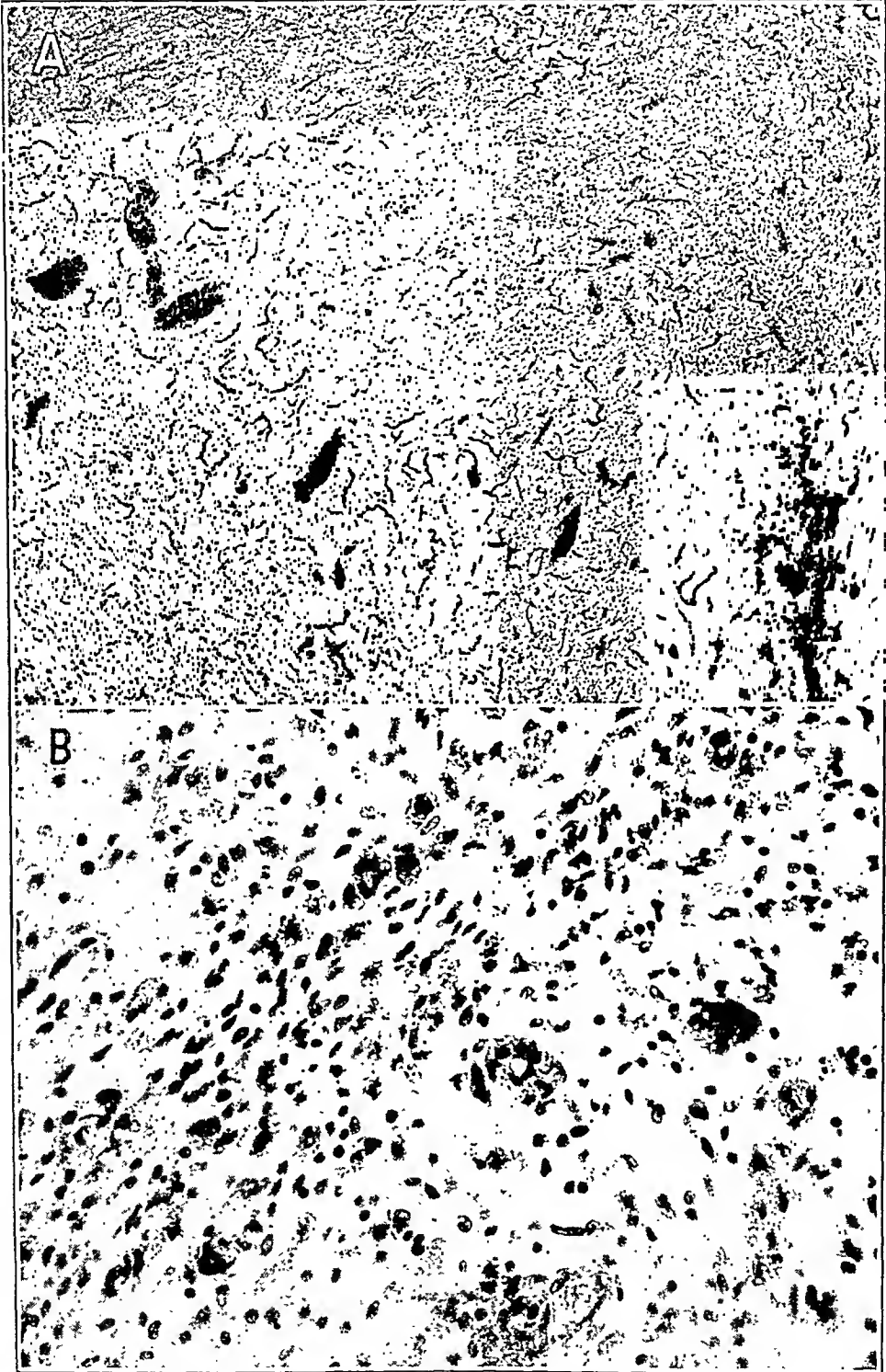


Fig. 3.—*A*, high power photomicrograph through area *F* in figure 2, showing the capillaries and venules engorged with red blood cells (stained black) and the diffuse demyelination. Weil stain. *B*, high power photomicrograph through the same focus stained by Nissl's method, showing the many blood pigment-filled histiocytes, particularly about the blood vessels.

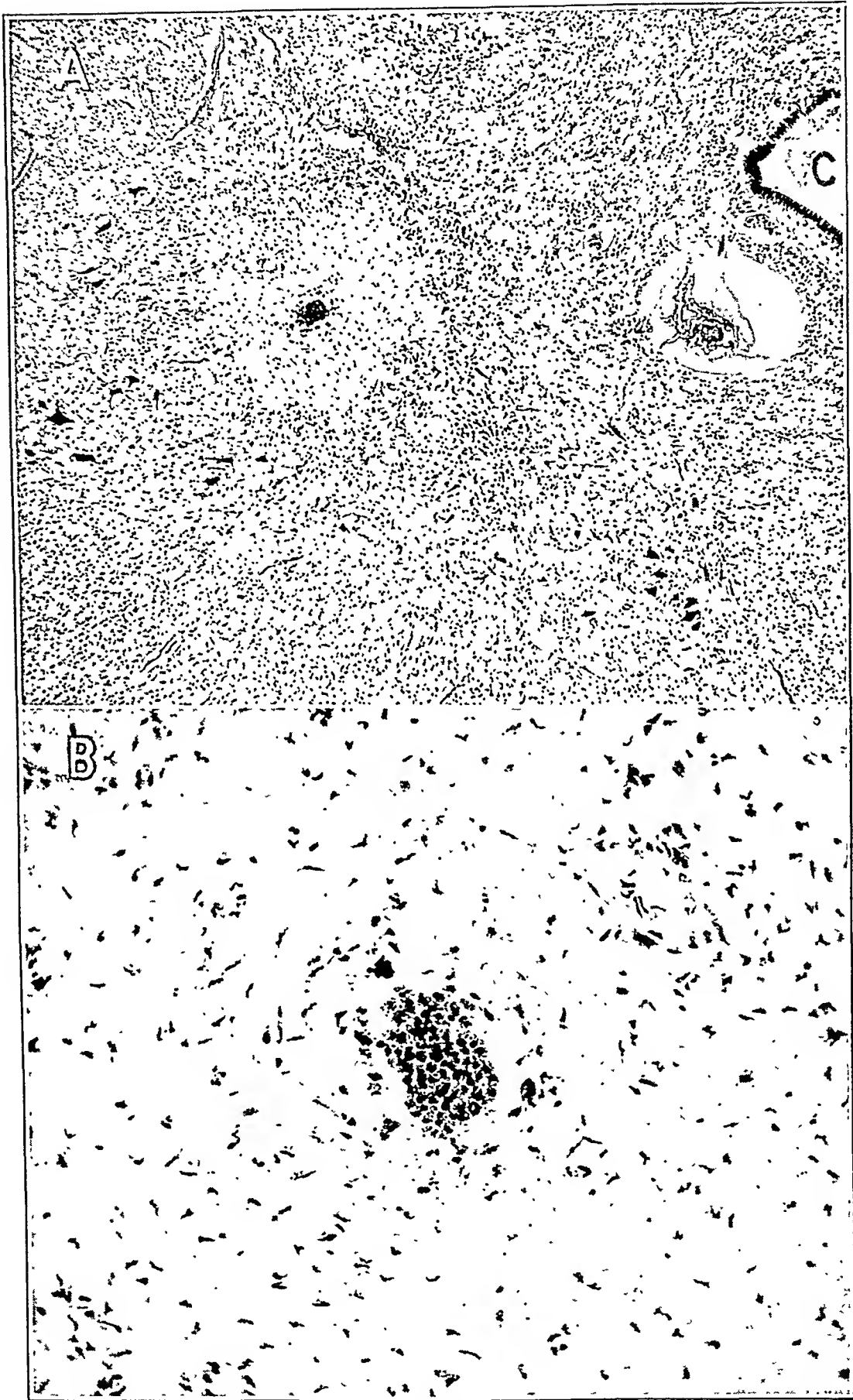


Fig. 4.—*A*, low power photomicrograph, showing a focus of degeneration in the gray substance of the cervical portion of the spinal cord. *C* is the central canal. *B*, high power photomicrograph of the focus seen in *A*, showing the central core of blood pigment-filled histiocytes surrounded by rod-shaped microglia cells. Toluidine blue stain.

In another series of cases the continuation of the process which leads to cavity formation could be followed. In the next stage of the evolution of the lesion disappearance of the ectodermal cellular elements, namely, the macroglia and the

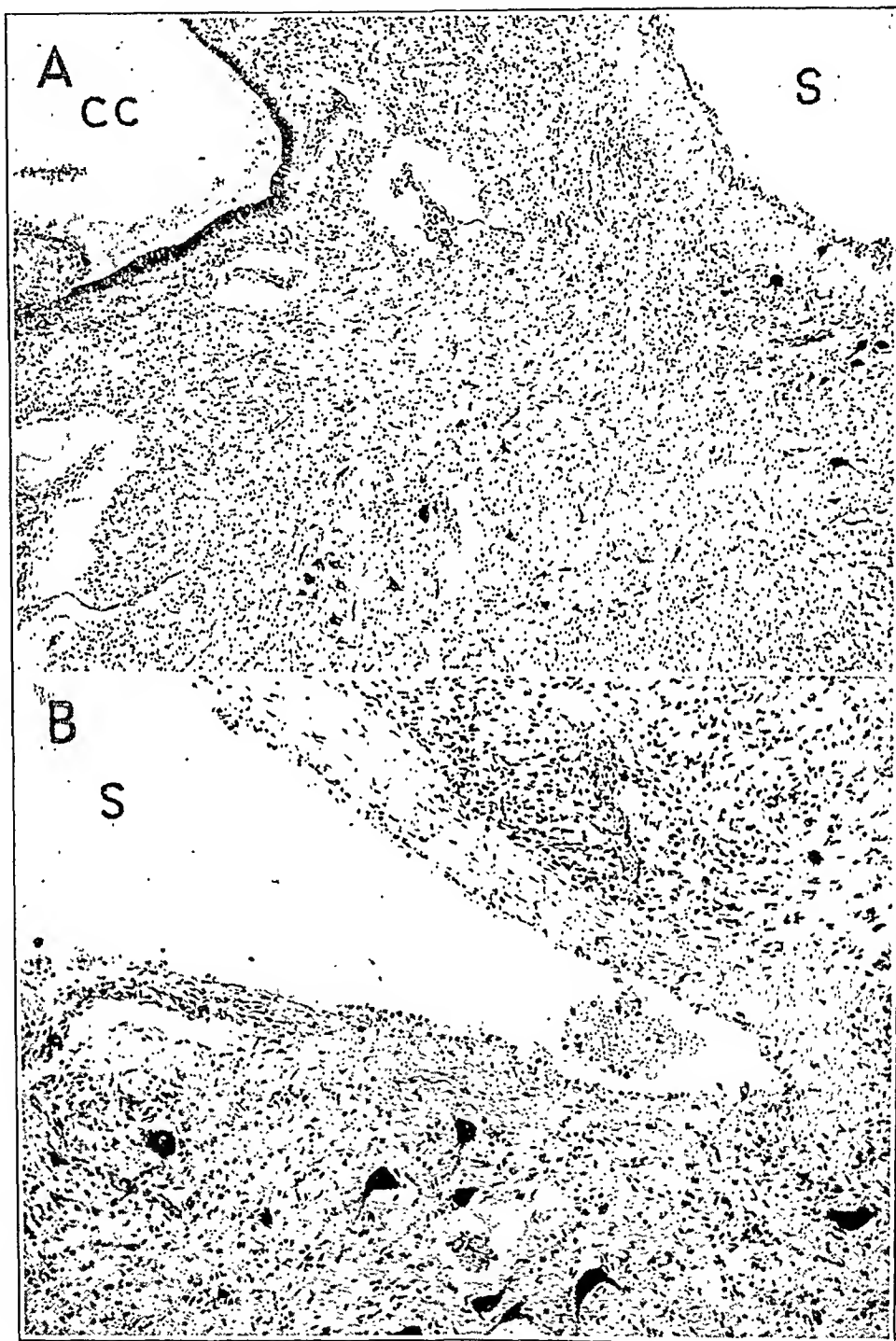


Fig. 5.—*A*, low power photomicrograph, showing the syrinx (*S*) bordering directly on the neural tissues. *CC* indicates the central canal. *B*, high power photomicrograph of syrinx (*S*). Toluidine blue stain.

ganglion cells, and breaking up of the nerve fibers were noted. At this stage the pathologic picture was characterized by a central core of histiocytes filled with

granules of blood pigment and surrounded by a wide zone rich in rod-shaped microglia cells (figs. 4 and 6 *A*). With the complete dissolution of the neurites and the neuroglial fibers, the affected area breaks down, resulting in a cavity (fig. 5). In many fields foci of histiocytes filled with blood pigment could be seen adherent to the wall of this cavity, which was lined by a zone of tissue composed almost exclusively of microglial elements. Special impregnations revealed that the lining contained neither connective nor glial tissue. In some levels the cavity extended into the anterior horns of the spinal cord, and occasionally a field rich in ganglion cells bordered on the cavity (fig. 5 *B*). Here and there, shrunken and deeply staining ganglion cells were seen, but in the unaffected areas they were of normal size and shape and rich in Nissl substance. The complete absence of satellitosis and neuronophagia was striking and characteristic. Occasionally this "syringomyelic" cavity was seen to communicate with a dilated central canal, with the resultant formation of a hydrosyringomyelic cavity (fig. 6 *B*). In such instances the hydromyelic portion, characterized by its lining of ependymal cells, contrasted with the "syringomyelic" portion, which was devoid of an epithelial lining but was surrounded by a zone rich in rod-shaped microglia cells.

Pathogenesis.—The pathologic process already described may be designated as liquefaction necrosis. This may result from a variety of states which affect the nutrition of the tissues of the central nervous system. Foremost among these pathologic states are vascular disturbances, and such, I believe, was the exciting cause here. The caudal migration of the hindbrain produced its impaction in the foramen magnum. The spinal arteries supplying the cervical portion of the spinal cord arise intracranially from the vertebral vessels. In their passage from the posterior cranial fossa into the spinal canal, they were compressed by the impaction of the hindbrain. The vertebral system of veins was similarly compressed, and this was evident in the cyanosis of the leptomeninges (fig. 1 *C*) and the extreme stasis of the blood in the capillaries and the venules of the cervical portion of the spinal cord (fig. 3 *A*). It is well known that sudden occlusion of a spinal artery may lead to malacia, as in the syndrome of the occlusion of the anterior spinal artery which I reported. Chronic ischemia, on the other hand, combined with venous stasis gives rise to a variety of pathologic states which may culminate in liquefaction necrosis. When the process undergoes a slow evolution many of the stages can be isolated and analyzed.

The cardinal features of this process are the progressive degeneration of the ganglion cells without satellitosis or neuronophagia, the disintegration of the macroglia cells and the nerve fibers with little gliosis, the early development of large numbers of microglia cells, which persist after all ectodermal tissues have disintegrated, and the final degeneration of the microglia cells themselves. The resultant cavity is lined neither with connective nor with glial tissue, and the surrounding tissues show no inflammatory reaction.

The pathologic changes are quite similar to those seen in some instances of chronic adhesive spinal arachnoiditis, as described so excellently by Schwarz,⁶ and more recently by Mackay.⁷ In this disorder the spinal arteries and the veins are enveloped by the fibroplastic thickening of the leptomeninx. Depending on the

6. Schwarz, E.: Syphilitische Myelomeningitis mit Hölenbildung im Rückenmarke und besonderen degenerativen Veränderungen der Neuroglia, Wien. klin. Wchnschr. **10**:177, 1897.

7. Mackay, R. P.: Chronic Adhesive Spinal Arachnoiditis, J. A. M. A. **112**:802 (March 4) 1939.

degree and rapidity of the process, a variety of pathologic states result, foremost among which is what Mackay termed anemic necrosis. As in the changes in the spinal cord associated with the Arnold-Chiari deformity, the absence of an inflammatory reaction, satellitosis, neuronophagia and the final cavity formation are characteristic of this process. I have termed the process "liquefaction necrosis," and as exciting causes I have emphasized the ischemia and the venous stasis.

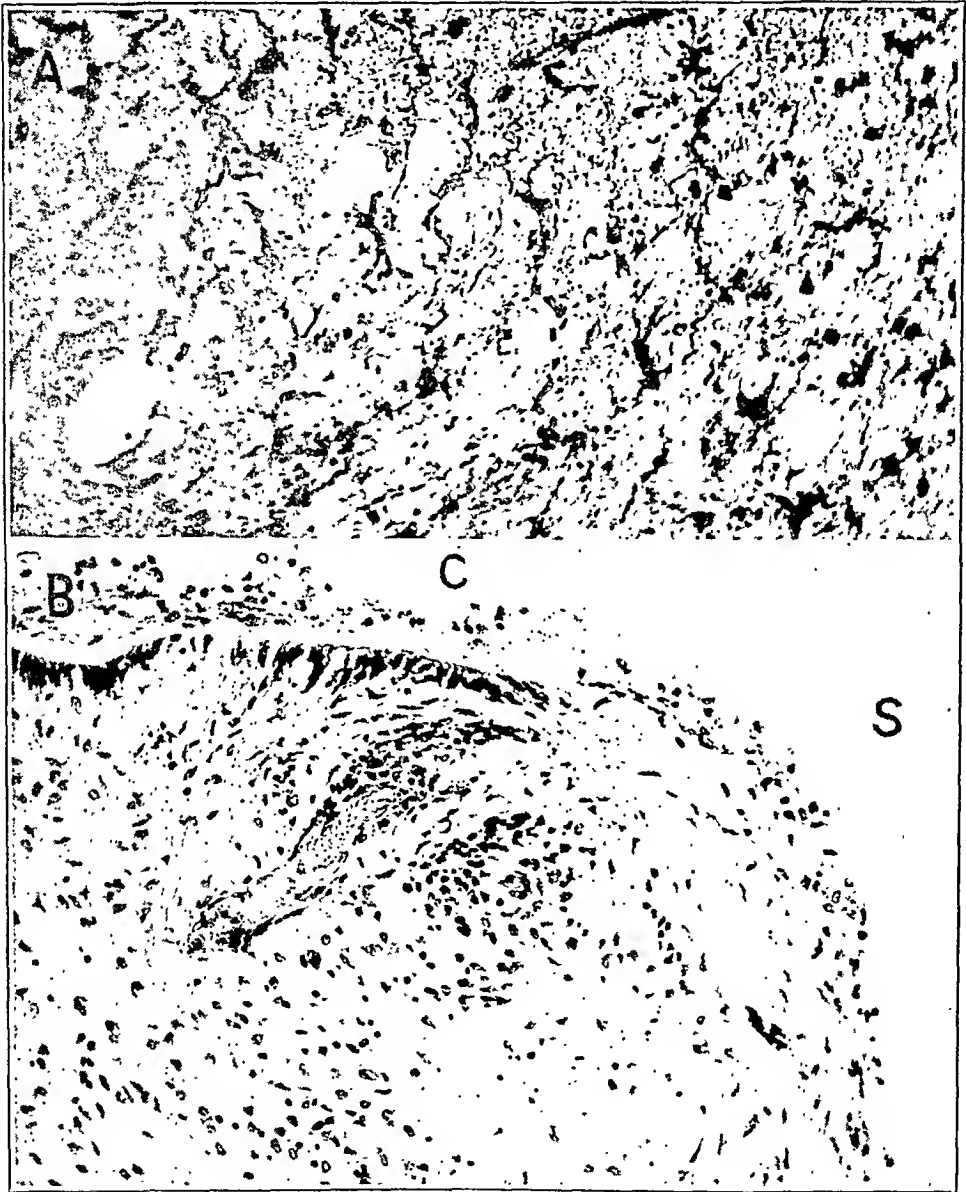


Fig. 6.—*A*, high power photomicrograph of the focus of degeneration, showing it to be composed of large numbers of microglia cells. Penfield's modification of Hortega's method. *B*, low power photomicrograph, showing the point where the pseudosyringomyelic cavity broke into the central canal. *C* indicates the central canal, and *S*, the syrinx. Toluidine blue stain.

Connective tissue was strikingly absent from the cavities; moreover, secondary gliosis occurs only in cases in which foci of incomplete degeneration develop and the astrocytes are proficient. This did not occur in my cases, in which the specimens were all from children who died under 1 year of age.

B. HYDROMYELIA AND PRESSURE EXPANSION

The cervical portion of the spinal cord in instances of Arnold-Chiari deformity may have cavities of an origin different from that described in the preceding condition. One is the hydromyelic cavity, which is easily recognized by virtue of its ependymal lining, and the other is a syringomyelic-like cavity. In many instances of the Arnold-Chiari deformity the choroid plexus is packed into the fourth ventricle

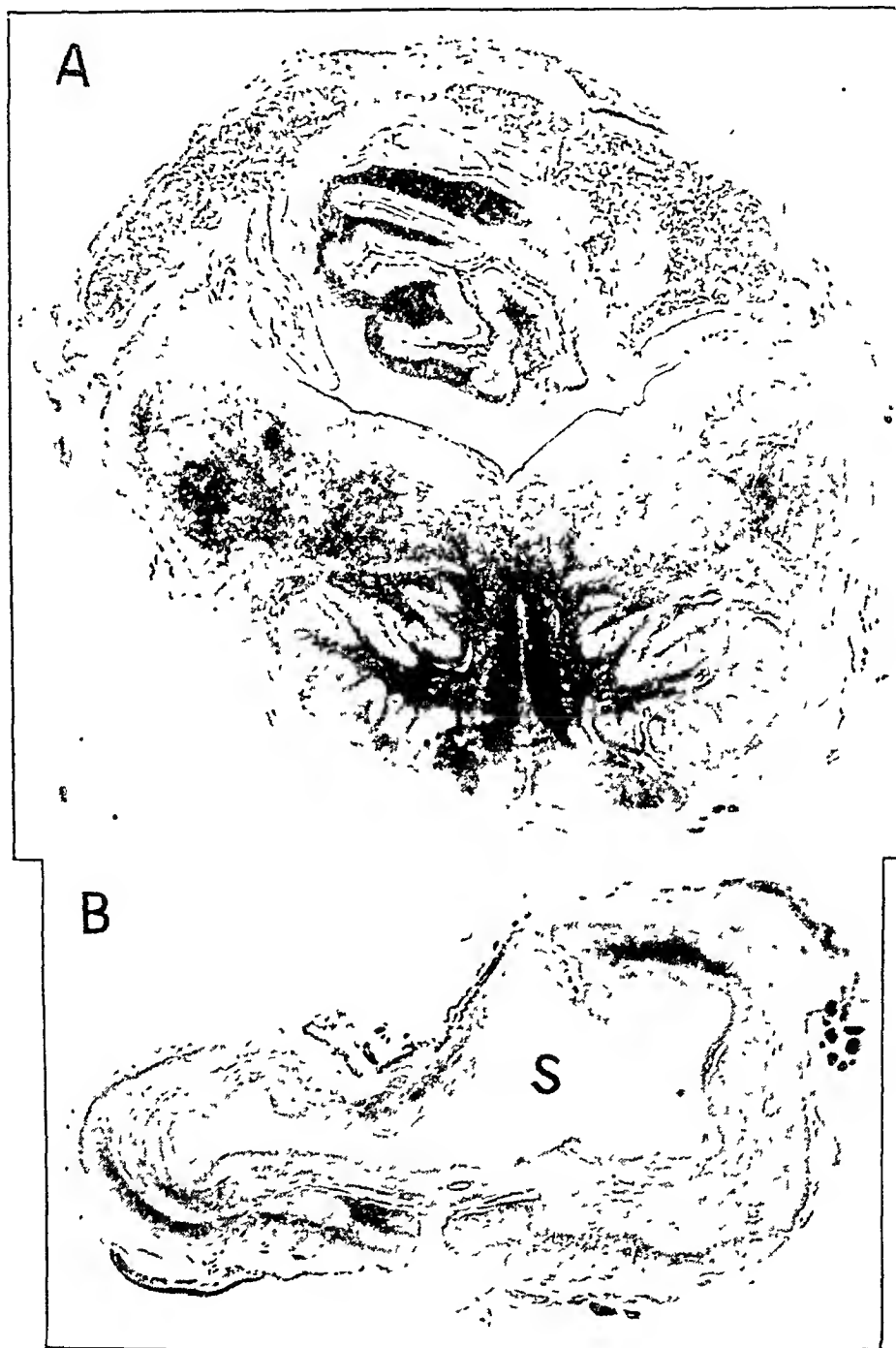


Fig. 7.—*A*, photomicrograph of a section through the neuraxis within the cervical portion of the canal (Arnold-Chiari deformity). *B*, photomicrograph of a section of the cervical portion of the spinal cord just below the Arnold-Chiari deformity, showing a large syrinx (*S*). Weil stain.

below the level of the foramen magnum (fig. 7 *A*). The constriction of the neuraxis by the bony ring prevents adequate communication between the caudal diverticulum of the fourth ventricle and the posterior cistern. The accumulating cerebrospinal fluid dilates the central canal and, in some instances, is associated with

perforation of the ependymal lining and the spread of the fluid into the posterior columns. The changes in such a case are schematically represented in figure 8, in which *S* indicates the syrinx. A transverse section through the cervical portion of the spinal cord at *E* is seen in figure 7 *B*, in which the syrinx lying posterior to the central canal resembles a syringomyelic cavity. This cavity bordered directly on substance of the spinal cord. The tissue lining the cavity contained no inflammatory elements, and the subjacent ganglion cells showed no evidences of satellitosis or neuronophagia. In contrast to the lining of the cavities in group A, microglia cells were absent. As in group A, the ischemia of the medullary substance may

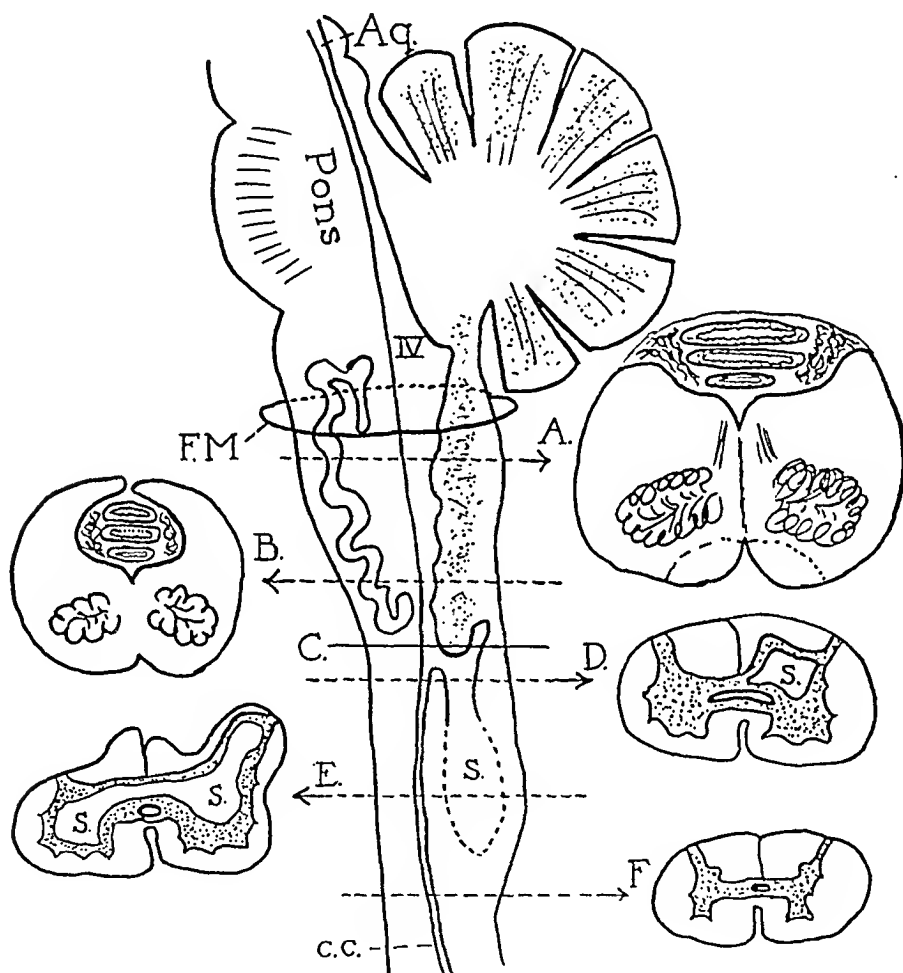


Fig. 8.—Schematic drawing of a midsagittal section through the hindbrain and upper cervical portion of the spinal cord from the case illustrated in figure 7. *F.M.* indicates the foramen magnum; *IV*, the fourth ventricle, and *S*, the syrinx. Level *A* corresponds to that in figure 7 *A*; level *E*, to that in figure 7 *B*. The brain was severed at *C*.

have played a role in the breaking down of the tissues and in the growth of the cavity, as well as in the increasing pressure within the central canal resulting from accumulating cerebrospinal fluid.

GROUP 2: MYELODYSPLASIC CAVITIES IN THE CERVICAL REGION

The state of spina bifida may involve the spinal cord, as well as the overlying meninges and the spinal column. The changes that may occur in the spinal cord

have been recently reviewed and described by me⁸ and are classified under the designation of myelodysplasia. Myelodysplastic changes usually occur underneath a bony defect, but in some instances extreme degrees of malformation have been unassociated with any evidence of spina bifida either overt or occult. In 1 instance of lumbosacral spina bifida the cervical portion of the spinal cord showed extreme degrees of myelodysplasia (fig. 9 *A*, *B* and *C*). At one level incomplete pseudoduplication was observed, with multiple enlarged and irregular canals lined by ependyma (fig. 9 *A*). As is usually the case, these canals were surrounded by large amounts of glial tissue. At an adjacent level the pseudoduplication was complete (fig. 9 *C*). At another level the central canal extended posteriorly, and its subependymal glia fused with the pia mater (fig. 9 *B*). In another case (fig. 9 *D*)

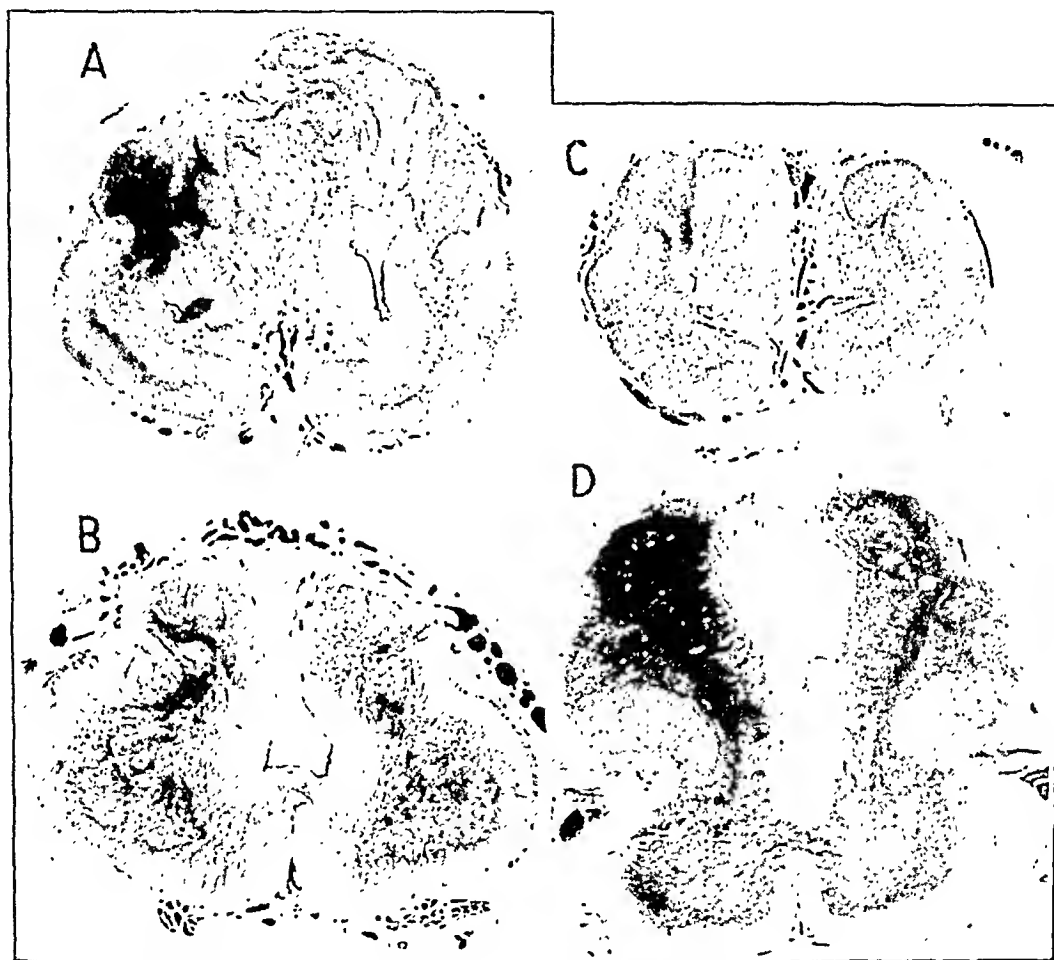


Fig. 9.—Photomicrographs illustrating myelodysplastic cavities. *A*, *B* and *C* are from the same case. In *A* and *C* varieties of pseudoduplication of the spinal cord are seen, and in *B* the central canal is enlarged and extends to the pia mater posteriorly. *D* illustrates myelodysplasia in the cervical portion of the spinal cord in another case. Weil stain.

the lower cervical portion of the spinal cord had an enlarged central canal, which as in the previous case, extended to the pia mater, and this canal was surrounded by an increased amount of glia tissue.

Comment.—Although the myelodysplastic tissues were otherwise unchanged in the 2 cases just cited, it is well known that such ependymal glia may undergo hyperplasia, break down, become invaded by connective tissue, be the seat of hemorrhages and, by the involvement of adjacent groups of ganglion cells and nerve fiber tracts, present the clinical picture of a progressive disorder. Since the central

8. Lichtenstein, B. W.: "Spinal Dysraphism": Spina Bifida and Myelodysplasia, Arch. Neurol. & Psychiat. 44:792 (Oct.) 1940.

portion of the spinal cord is involved, the clinical picture may be indistinguishable from that produced by true syringomyelia. The Klippel-Feil syndrome (*brevicollis*), which anatomically is a variety of spina bifida characterized by fusion of the bodies of the cervical vertebrae, may be associated with the Arnold-Chiari deformity, myelodysplasia of the cervical portion of the spinal cord or even true syringomyelia, and as a result the differential diagnosis by means of clinical examination, even combined with operative inspection, may be difficult.

GROUP 3: PLATYBASIA AND "SYRINGOMYELIA"

Platybasia is essentially a deformity of the posterior portion of the base of the skull. Although there is no universal agreement as to its origin, there is evidence that it is analogous to spina bifida, which is the anatomic expression of delayed or defective development of the bony structures about the spinal cord. The anatomic link between classic spina bifida and platybasia is, I believe, found in the Klippel-Feil complex, in which, as in platybasia, deformities and anomalies occur in the atlas and the axis.

The deformity of the base of the skull which characterizes platybasia is a flattening of the inclined plane formed by the clivus. As a result, the foramen magnum is often described as being pushed up into the inferior cranial fossa, and it is also usually small, misshapen or eccentrically placed. This may be associated with occipitalization of the atlas. The ascent of the foramen magnum may result in the localization of the structures of the hindbrain in the foramen magnum or in the upper cervical portion of the spinal canal rather than in their normal location—the posterior cranial fossa. The appearance of the tonsils of the cerebellum in the upper cervical portion of the spinal canal is, many times, not unlike that of the Arnold malformation (of the Arnold-Chiari complex), resulting from fixation of the spinal cord in spina bifida.

Platybasia was described in detail by Virchow⁹ in 1876 and by Grawitz¹⁰ in 1880. The neurologic significance of platybasia has become increasingly prominent of late, and Gustafson and Oldberg¹¹ have recently reviewed the subject and described 5 additional cases.

In such cases signs of syringomyelia may develop from the following factors: (1) pressure of the deformed bony ring or of the dens epistrophei on the neuraxis; (2) vascular changes (stasis; ischemia) resulting from compression of the spinal arteries and the vertebral system of veins; (3) pressure of the Arnold-Chiari deformity; (4) proliferations or degenerations of subependymal glial tissue in a coexistent myelodysplastic spinal cord; (5) true syringomyelia coexisting with platybasia and the Arnold-Chiari deformity, and (6) direct pressure of the bony structures or vascular insufficiency, accentuating the symptoms produced by a preexisting lesion of the spinal cord, such as syringomyelia or myelodysplasia.

The lack of continued improvement after decompression of the foramen magnum for relief of platybasia or the progressive development of the syringomyelic state after such an operation may be the result of coexisting syringomyelia, as in case 3 reported by Gustafson and Oldberg. With their permission, I review that case here.

9. Virchow, R.: *Beiträge zur physischen Anthropologie der Deutschen mit besonderer Berücksichtigung der Friessen*, Berlin, G. Vogt, 1876; cited by Gustafson and Oldberg.¹¹

10. Grawitz, P.: *Beitrag zur Lehre von der basillaren Impression des Schädels*, Virchows Arch. f. path. Anat. 80:449, 1880.

11. Gustafson, W. A., and Oldberg, E.: Neurologic Significance of Platybasia, Arch. Neurol. & Psychiat. 44:1184 (Dec.) 1940.

A Negress aged 46 complained of weakness of both hands and forearms of two years' duration. Shortly after the onset the weakness spread into the left lower extremity. One year later numbness of the hands developed. The essential neurologic changes were: pronounced atrophy of the thenar and hypothenar eminences bilaterally and anesthesia, analgesia and thermanesthesia from the third cervical segment to the sixth thoracic segment on the right side.

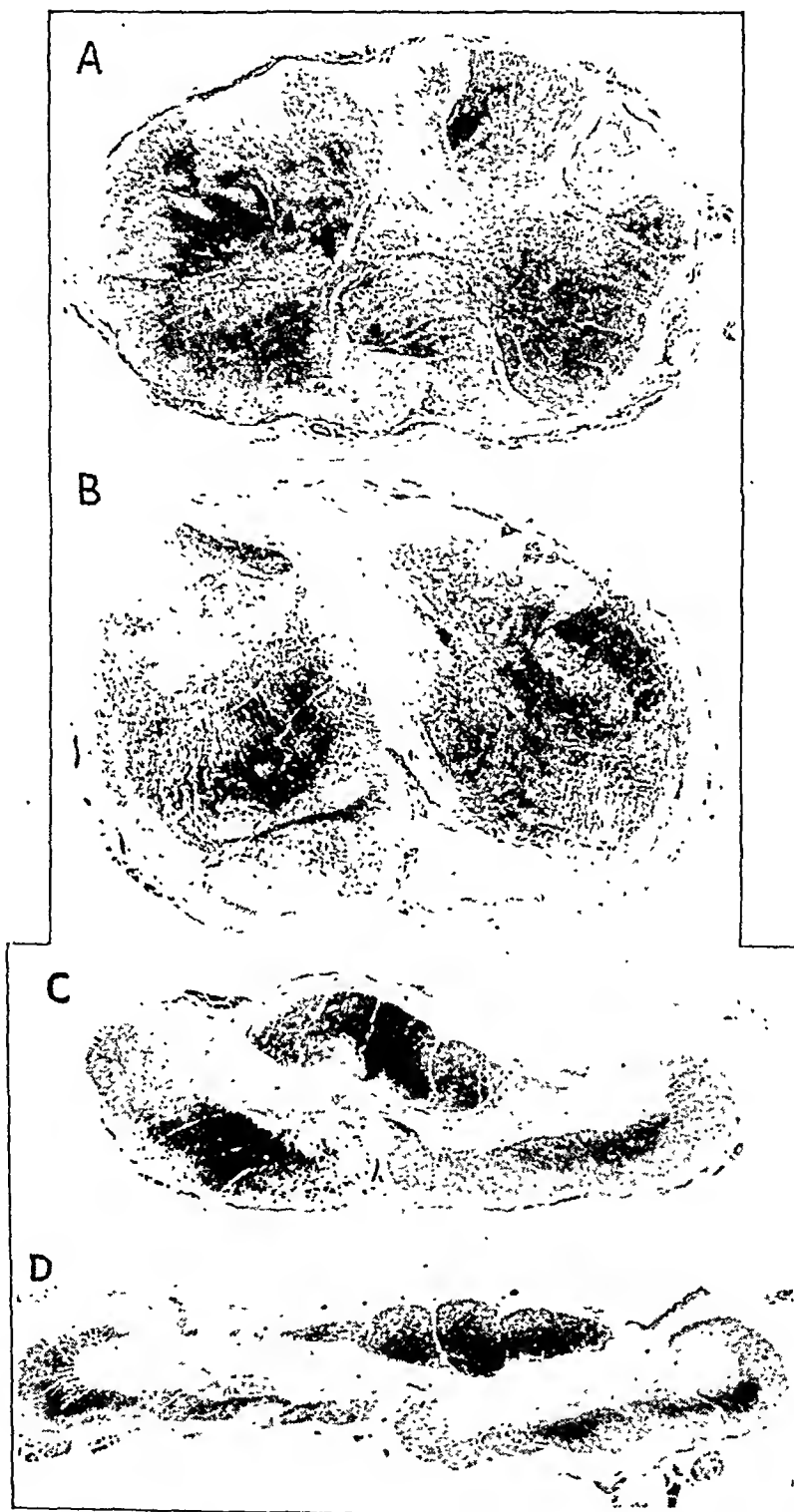


Fig. 10.—Photomicrographs through various levels of the spinal cord in the case of platybasia complicated by syringomyelia which is described in the text. In *A* and *B* myelodysplastic changes are seen, while in *C* and *D* the characteristic features of true syringomyelia are evident. Weil stain, counterstained by van Gieson's method.

Roentgen examination revealed occipitalization of the first cervical vertebra, with notable decrease in the anteroposterior diameter of the foramen magnum.

At operation the arch of the atlas was observed to be fused to the occipital bone and, on exposure of the dura mater, a definite constriction ring was seen at the level of the foramen magnum. When the dura mater was opened, the upper cervical portion of the spinal cord was observed to be smaller than normal.

At the time of discharge, on the twentieth postoperative day, subjective improvement was noted, but it was difficult to evaluate the change objectively. Later cystitis and pyelitis developed, and the patient died, three months after the operation.

At autopsy a sharp constriction ring was seen on the neuraxis corresponding to the site of the foramen magnum. Thorough microscopic examination of the spinal cord and the brain stem was made. A section taken from the site of the constriction showed myelodysplastic changes in the nature of proliferation of the central ependymal cells (fig. 10 *A*). At a level just rostral to the constriction (fig. 10 *B*) the hind end of the fourth ventricle was seen to be elongated and slitlike. Sections through the middle cervical region of the spinal cord (fig. 10 *C* and *D*) showed the classic changes of true syringomyelia.

In this case the clinical symptoms were indicative of an intramedullary lesion of the cervical portion of the spinal cord—syringomyelia. The roentgenographic evidence of platybasia and the operative evidence of constriction of the neuraxis at the foramen magnum, however, were sufficient to make one think that the intramedullary disorder resulted from pressure, ischemia and venous stasis (group 1). The reason for the lack of continued improvement after decompression, however, became apparent in the discovery of a complicating pathologic process—syringomyelia. I believe that the compression at the foramen magnum, together with its associated vascular disturbance, did play a role in accentuating the syringomyelic syndrome, but since this contribution pertains to the changes in the neuraxis resulting from or complicating constriction at the foramen magnum, I do not wish here to discuss that controversial subject—the pathogenesis and pathology of true syringomyelia.

SUMMARY AND CONCLUSIONS

Compression of the neuraxis at or about the region of the foramen magnum may result in the degeneration of the central portion of the cervical portion of the spinal cord, with the production of a syringomyelia-like state.

Impaction of the Arnold-Chiari deformity in the foramen magnum may result in circulatory disturbance and subsequent degeneration of the neural tissues by pressure on the spinal arteries and veins at the level of the foramen magnum.

Deformities of the base of the skull, the foramen magnum, the atlas and the axis (platybasia) may result in constriction of the neuraxis, and degenerative changes in the adjacent spinal cord may result directly from pressure of the bones on the neural tissues or indirectly from ischemia due to interference with the circulation in the spinal arteries and veins.

Platybasia, the Klippel-Feil deformity and spina bifida may be associated with myelodysplastic changes in the spinal cord, and in cases of such a deformity involvement of the ganglionic cell groups and nerve fibers, by reactions (such as degeneration and proliferation) in the myelodysplastic tissue, may result in the clinical picture of syringomyelia.

True syringomyelia may be coexistent with platybasia and spina bifida, and the clinical picture may be due to the primary disorder in the spinal cord rather than to the roentgenographically visible changes in the bone.

Platybasia and the Arnold-Chiari deformity, by pressure on the spinal cord and on the spinal arteries and veins, may accentuate the syringomyelic syndrome resulting from myelodysplastic changes in the cord or true syringomyelia and the lack of continued improvement after decompression of the neuraxis may be due to the associated disorders of the spinal cord.

Case Reports

PERMANENT DAMAGE TO THE NERVOUS SYSTEM FOLLOWING AN ATTACK OF POLYRADICULONEURITIS (GUILLAIN-BARRÉ SYNDROME)

Report of a Case, with Necropsy

WILLIAM O. RUSSELL, M.D., AND WALTER L. MOORE, M.D., ST. LOUIS

Polyradiculoneuritis is a well recognized neurologic syndrome characterized by widespread motor and sensory signs pointing to involvement of the spinal and cranial nerves (most commonly the seventh cranial nerve). The definitely increased protein content of the cerebrospinal fluid without any change in the number of cells (albuminocytologic dissociation) is regarded as characteristic of the disorder and an important diagnostic feature. On the basis of the clinical symptoms the disease appears to be a distinct entity, but no etiologic agent has been established. That a virus is the causative agent has been repeatedly suspected, and an early report¹ described transmission of the disease to monkeys. All subsequent work, however, has failed to substantiate this earlier claim, although the idea that the syndrome is an acute infectious disease generally prevails.²

Clinically, polyradiculoneuritis is characterized by the onset of progressively severe neurologic signs and symptoms, which may continue to a fatal termination, usually within two weeks. Gradual improvement is seen in the majority of cases, however, with the patient showing complete, or nearly complete, recovery of all the lost neurologic functions in from six months to a year. The mortality rate is high, varying in different series from 14 to 42 per cent.³ The pathologic changes in the nervous system in patients who died during the acute phase of the disease have been well studied.⁴ Degeneration affecting the myelin sheaths and axis-cylinders, occasionally with a slight inflammatory reaction, is consistently observed in the peripheral nerves. Questionable pathologic changes in the ganglion cells without inflammatory reaction have been reported. Visceral lesions resembling those seen in such diseases as diphtheria and typhoid fever have been recently described² in patients who died during an acute attack.

Knowledge of pathologic changes in the nervous system in persons who have recovered from an attack of polyradiculoneuritis is lacking, since only a small number of such patients show clinical evidence of permanent damage to the nervous system. The following communication is a clinical and pathologic report of a case

From the Department of Pathology, Washington University School of Medicine, and the St. Louis County Hospital.

1. Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, *Quart. J. Med.* **12**:88-126, 1919.

2. Cobb, S., and Coggeshall, H. C.: Neuritis, *J. A. M. A.* **103**:1608-1617 (Nov. 24) 1934. Sabin, A. B., and Aring, C. D.: Visceral Lesions in Infectious Polyneuritis (Infectious Neuronitis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome, Landry's Paralysis), *Am. J. Path.* **17**:469-482, 1941.

3. Roseman, E., and Aring, C. D.: Infectious Polyneuritis; Infectious Neuronitis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome, Landry's Paralysis, etc., *Medicine* **20**:463-494, 1941.

4. (a) Casamajor, L.: Acute Ascending Paralysis Among Troops: Pathologic Findings, *Arch. Neurol. & Psychiat.* **2**:605-620 (Dec.) 1919. (b) Viets, H. R.: Acute Polyneuritis with Facial Diplegia, *ibid.* **17**:794-803 (June) 1927. (c) Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathologic Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, *ibid.* **35**:937-963 (May) 1936. (d) Honeyman, W. M.: Pathological Study of a Group of Cases Sometimes Referred to as Polyneuritis, *Bull. Neurol. Inst. New York* **6**:519-528, 1937. (e) Bradford, Bashford and Wilson.¹ (f) Roseman and Aring.³

of polyradiculoneuritis in which recovery from the acute phase of the disease was followed by neurologic signs indicating permanent and significant damage to the nervous system. The patient died nineteen months after the initial attack of intussusception of the small intestine, so that we were offered the singular opportunity of studying the pathologic changes in the nervous system caused by this obscure neurologic disease. We have been unable to find a report of so clearly established a case of polyradiculoneuritis with permanent damage to the nervous system in which pathologic studies were made.

REPORT OF CASE

History.—A single white man aged 32, American, a gardener, entered the St. Louis County Hospital on Sept. 15, 1941. He had been well and active until May 1940, when he first noticed numbness of his lower extremities. For an indefinitely known period before the onset of the numbness he had experienced some tingling sensation in both feet. Two weeks after the onset of the numbness in his legs he noted difficulty in walking, which was accompanied by considerable weakness of his legs. Simultaneously with the onset of weakness in the legs he noted progressive loss of motor power in the upper extremities, which was also accompanied by a tingling sensation and numbness. The symptoms in the upper extremities, however, were always less severe than those in the legs. Because these symptoms had become progressively worse, until he could walk only with assistance from another person, he was admitted to the St. Louis County Hospital on May 14, 1940, just six weeks after the onset of the numbness in his legs. At that time he stated that he had lost an indefinitely known amount of weight since the onset of his illness. He denied having had an infection of the respiratory tract or other infectious disease coincident with or preceding the onset of his neurologic symptoms.

He was pointedly questioned concerning a history of venereal infection. This he denied by name and symptoms, and there was no history of antisyphilitic treatment. The patient stated, and the assertion was confirmed by his family, that prior to his present illness he had always had good health and had never used alcohol in any form. His diet had been adequate, a fact also confirmed by his family.

Physical Examination on First Admission.—The patient was well developed but poorly nourished and unable to stand alone. The pupils were equal and regular, and both reacted normally to light and in accommodation. There was pronounced incoordination of voluntary movements, with manifest loss of motor power and hypotonia of the muscles of all the extremities. Examination of the cranial motor nerves revealed a normal status. The deep tendon reflexes were absent in the lower extremities but were present in the upper extremities, although definitely diminished. Pain, temperature, light touch and vibration sensibilities were absent in the lower extremities. Delayed hyperesthesia was noted on stroking the soles of the feet, and delayed myalgia was present in the calf muscles of both legs. Extension of the leg on the flexed thigh produced severe pain. Sensory examination of the upper extremities gave essentially normal results except for myalgia and tenderness over the large nerve trunks. A pathologic toe sign and clonus were not elicited, and all the superficial reflexes were present.

Course in Hospital and Treatment.—Lumbar puncture performed on the day of entry disclosed a clear spinal fluid, which did not appear to be under increased pressure. There were only 4 cells per cubic millimeter of fluid; the Pandy reaction for globulin was negative, and the total protein was 117 mg. per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative, and the colloidal gold curve was 0022210000. Other laboratory data were as follows: The urine was normal except for a trace of albumin; the erythrocyte count was 3,850,000, with 11.5 Gm. of hemoglobin per hundred cubic centimeters (67 per cent); the white blood cell count was 6,800, and the differential cell count was normal. The Hinton and Kline reactions of the blood were negative. Gastric analysis showed 40 per cent total acidity and no free hydrochloric acid in the fasting specimen. Free hydrochloric acid was present in the second specimen but not in the third. The total acidity of the third specimen was 20 per cent.

With the history of an acute onset of motor weakness and sensory disturbances, indicating severe involvement of the peripheral nerves, and the finding in the spinal fluid of a significantly increased total protein content with a normal cell count (albuminocytologic dissociation), the diagnosis of polyradiculoneuritis (Guillain-Barré syndrome) was made.

During the first five days of hospitalization the neurologic signs observed on entry became progressively worse, and slurred speech and mental apathy developed. On May 19, just five

days after entry to the hospital, the patient suddenly lost his vision; this was followed five hours later by a generalized convulsion. Although ophthalmoscopic examination the following day showed normal fundi and the pupillary reactions were normal, he still could not see. Neurologic examination at that time disclosed complete quadriplegia, with paralysis of the left facial nerve of peripheral type.

Two days later, on May 21, although the patient's vision had returned, there was no manifest improvement of his general condition. Further improvement was not observed until June 1. At this time a slight return of motor power in both upper and lower extremities was noticed.

Examination of the spinal fluid, removed by lumbar puncture on June 4, disclosed a total protein content of 142 mg. per hundred cubic centimeters of fluid and only 3 cells per cubic millimeter. On June 10 the paralysis of the left side of the face was less apparent, and the slurred speech had disappeared. Improvement continued during the next ten days, so that on June 20 he was able to sit up in a chair. Examination of the spinal fluid on June 19 showed only 100 mg. of protein per hundred cubic centimeters and a total cell count of 5 per cubic millimeter. At this time he had no paresthesias, and there was a fair return of the motor strength in his extremities. Examination of the cranial motor nerves revealed only slight impairment of the seventh nerve, as manifested by a slight droop of the left side of the mouth. The pupils were equal, regular and circular in outline, and both reacted normally to light and in accommodation. The deep tendon reflexes were absent in the lower extremities, but were present in the upper extremities, although greatly diminished. All forms of sensation had returned except vibratory sensibility, which was still absent in the lower extremities. The Romberg sign was positive.

The patient was discharged from the hospital on July 25. For over a month before discharge he had sat up daily for long periods and had walked with assistance from a hospital attendant. Neurologic examination at the time of discharge disclosed the same signs as those observed on June 20.

Except on the first two days of his hospitalization, he had received a high vitamin and high caloric diet. After the onset of quadriplegia this was supplemented by the oral and parenteral administration of preparations of the vitamin B complex, with the addition of alpha tocopherol after May 25. His entire course in the hospital was afebrile. The pulse rate was elevated, varying from 74 to 120 beats per minute and averaging about 100 beats. His respirations, however, were always normal, and at no time during his stay in the hospital was there retention or incontinence of urine or feces.

The final clinical diagnosis was polyradiculoneuritis (Guillain-Barré syndrome), with degeneration of the posterior column of the spinal cord.

Interval History.—From August 1940 until August 1941 the patient was followed in the outpatient neurologic clinic; during this time slight improvement was noted in his neurologic condition. On his last visit to the clinic, on August 21, neurologic examination showed loss of all the deep tendon reflexes, with loss of vibration and position sensibility in both upper and lower extremities. There was severe ataxia of the upper and lower extremities, and the Romberg sign was positive.

Second Admission.—The second, and final, admission to the hospital was on Sept. 15, 1941. For two days prior to entry he had complained of abdominal pain and had vomited several times when he attempted to eat. During this period he was unable to retain anything taken by mouth and complained of obstipation. Because he had become so weak from not being able to eat and his abdominal pain continued unabated, he was brought into the hospital.

Physical Examination.—The patient was well developed but poorly nourished and dehydrated. The abdomen was moderately distended, and the percussion note was tympanitic, except in the right lower quadrant. No masses were palpated. The neurologic signs were similar to those noted on the last visit to the outpatient clinic, on August 21.

Laboratory Examination.—A leukocyte and a differential blood count, done on September 16, were normal. The erythrocyte count at that time was 2,750,000, and the hemoglobin content was 58 per cent, with a color index of 1. The reactions to the Kahn and Hinton tests were negative. Urinalyses, done on September 16 and September 18, revealed only a 4 plus reaction for sugar on the latter date, after the intravenous administration of a large amount of dextrose. The nonprotein nitrogen content of the blood on September 16 was 63 mg. per hundred cubic centimeters.

Course in Hospital and Treatment.—With the history of vomiting, obstipation and abdominal pain, the diagnosis of carcinoma of the gastrointestinal tract with obstruction was considered, and fluids were given intravenously for the patient's dehydration. The abdominal

pain continued during the next two days, and he vomited frequently. On September 16 a soft mass that was not sharply outlined was palpated on rectal examination above the prostate. The same day his condition became more acute and was marked by increasingly severe cramping abdominal pain and the vomiting of large amounts of greenish liquid material. At this time he became stuporous. A surgical consultant suggested a diagnosis of cancer of the gastrointestinal tract with partial obstruction but advised against operation at that time because of the patient's poor condition. The patient died the following day, September 18, after a period of profound restlessness, irrational talking and, finally, coma.

The clinical diagnoses were carcinoma of the gastrointestinal tract, with obstruction and low grade peritonitis, and degeneration of the posterior column of the spinal cord following polyradiculoneuritis.

Necropsy.—Examination was performed nine hours after death. The lungs, pancreas, kidneys, adrenals, bladder, aorta and bone marrow were grossly not remarkable. The significant observations were as follows:

The abdomen was moderately distended, and there was a slight pitting edema of the lower extremities. The peritoneal cavity contained 1,500 cc. of serosanguineous fluid. There was an intussusception involving approximately 40 cm. of the small intestine 180 cm. above the ileocecal valve. The stomach and the small intestine above the intussusception were greatly dilated and filled with greenish brown liquid feces. The serosal surface of the dilated intestine showed small petechiae and was covered with fine shreds of fibrin. The invaginated segment of intestine was gangrenous, deep black-red and covered with fine shreds of fibrin. Careful examination of the invaginated portion and the adjoining segments of intestine disclosed no adhesions, tumor or diverticulum that in any way could have been a factor in causing the intussusception. The gastrointestinal tract below the intussusception was normal and contained only a small amount of formed brown feces. A small amount of the greenish brown liquid fecal material observed in the stomach was noted also in the trachea and bronchi. Scattered petechiae were seen on all the serous surfaces and beneath the endocardium of the left ventricle. Histologic examination of the abdominal and thoracic organs confirmed the gross pathologic observations.

Examination of the Nervous System.—The weight of the brain was normal, being 1,250 Gm. The external configurations, leptomeninges, basilar arteries and successive sections through the brain showed no gross pathologic change. The entire spinal cord, removed with the dura mater and spinal ganglia attached, was grossly not remarkable.

Sections were taken for microscopic study from the cortex of the frontal, parietal and occipital lobes; the cornu ammonis; the caudate and lentiform nuclei; the mesencephalon; the medulla oblongata; the lumbar, thoracic and cervical levels of the spinal cord; the spinal ganglia; the cauda equina, and the sciatic nerve. All the sections from the brain were stained with hematoxylin and eosin, Kultschitzky's stain for myelin sheaths and phosphotungstic acid hematoxylin. No pathologic changes were seen in any of the sections of the brain. A section stained with cresyl violet taken through the nucleus of the seventh cranial nerve, in the medulla oblongata, disclosed no pathologic changes in the ganglion cells. The ganglion cells contained a moderate amount of lipochrome pigment, which was not regarded as pathologic. No pathologic change was observed in the ganglion cells or the glia cells of the nucleus gracilis or nucleus cuneatus in sections taken from the caudal part of the medulla oblongata. Pathologic changes were observed in sections from the spinal cord, spinal ganglia, peripheral nerve and cauda equina.

Spinal Cord: Sections taken from the cervical, thoracic and lumbar levels of the cord and stained by the Kultschitzky method for myelin all showed nearly complete loss of myelinated nerve fibers in the posterior column. In the section taken from a lumbar segment the loss of myelinated fibers in the peripheral part of the posterior column and a narrow zone adjacent to the posterior gray commissure was less severe than in other areas of the posterior column (fig. 1A). Small parts of the posterior roots included in the sections likewise showed an extensive loss of myelinated nerve fibers, with only a few fibers remaining. There was no manifest loss of the myelinated fibers in the anterior and lateral columns and in the anterior roots.

In frozen sections stained by the sudan III method for fat, numerous large macrophages containing fat were noted in the posterior column (fig. 1B). Sections of the spinal cord stained with cresyl violet disclosed the usual number of ganglion cells, without pathologic change in the anterior or posterior roots or in Clarke's column. A slight increase in the number of glial nuclei was seen in the posterior column. In none of the sections of the spinal cord was there evidence of acute or chronic inflammation, either in the leptomeninges or in the nerve tissue.

Spinal Ganglia: There was a moderate decrease in the number of ganglion cells seen in sections taken from three dorsal root ganglia. Many of the cells were atrophic and were surrounded by an increased number of large periganglionic cells. Large groups of the periganglionic cells were arranged in concentric form. In certain instances they enclosed a small, homogeneously basophilic-staining material, presumably a part of a degenerated ganglion cell. There was no evidence of acute or chronic inflammation.

Peripheral Nerve: A few scattered macrophages filled with fat were observed in a frozen section of the sciatic nerve stained with sudan III. In sections stained with hematoxylin

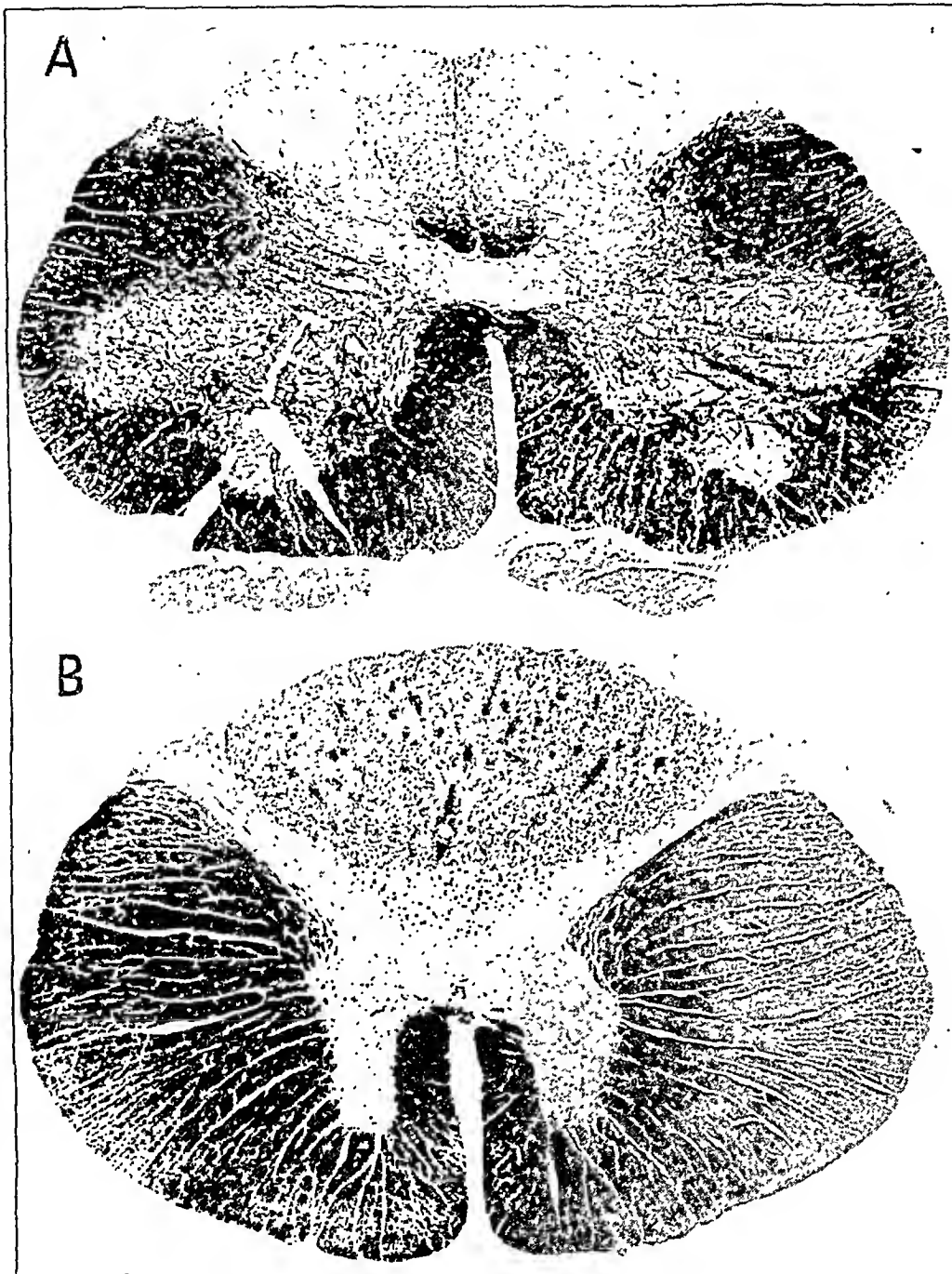


Fig. 1.—*A*, section of the spinal cord from a lumbar segment. Note the extensive loss of myelinated nerve fibers in the posterior column. Kultschitzky's stain for myelin sheaths; $\times 12$. *B*, section from the thoracic level of the cord. The fine black dots seen in the posterior column are macrophages filled with fat. Sudan III stain for fat; $\times 14$.

and eosin there was a moderate increase in the number of fibroblastic nuclei, and in sections prepared with the Bodian silver method for nerve fibrils there was readily apparent reduction in the number of axis-cylinders.

Cauda Equina: Sections stained for myelin showed an extensive reduction in the number of myelinated fibers in the sensory roots (fig. 2*A*). The motor roots, however, appeared normal (fig. 2*B*). Sections stained with phosphotungstic acid hematoxylin revealed a large

amount of brownish red-staining collagen in the sensory roots and an unusually large number of fibroblastic nuclei. The motor roots contained only a slight amount of brown-red collagen and the usual number of blue-staining myelinated nerve fibers.

Anatomic Diagnosis.—The anatomic diagnosis was intussusception of the small intestine, with complete obstruction and gangrene of the intussuscepted segment; generalized serosanguineous peritonitis, and degeneration of the ganglion cells in the posterior root ganglia, with degeneration of the posterior column of the spinal cord, the posterior roots and the peripheral nerves.

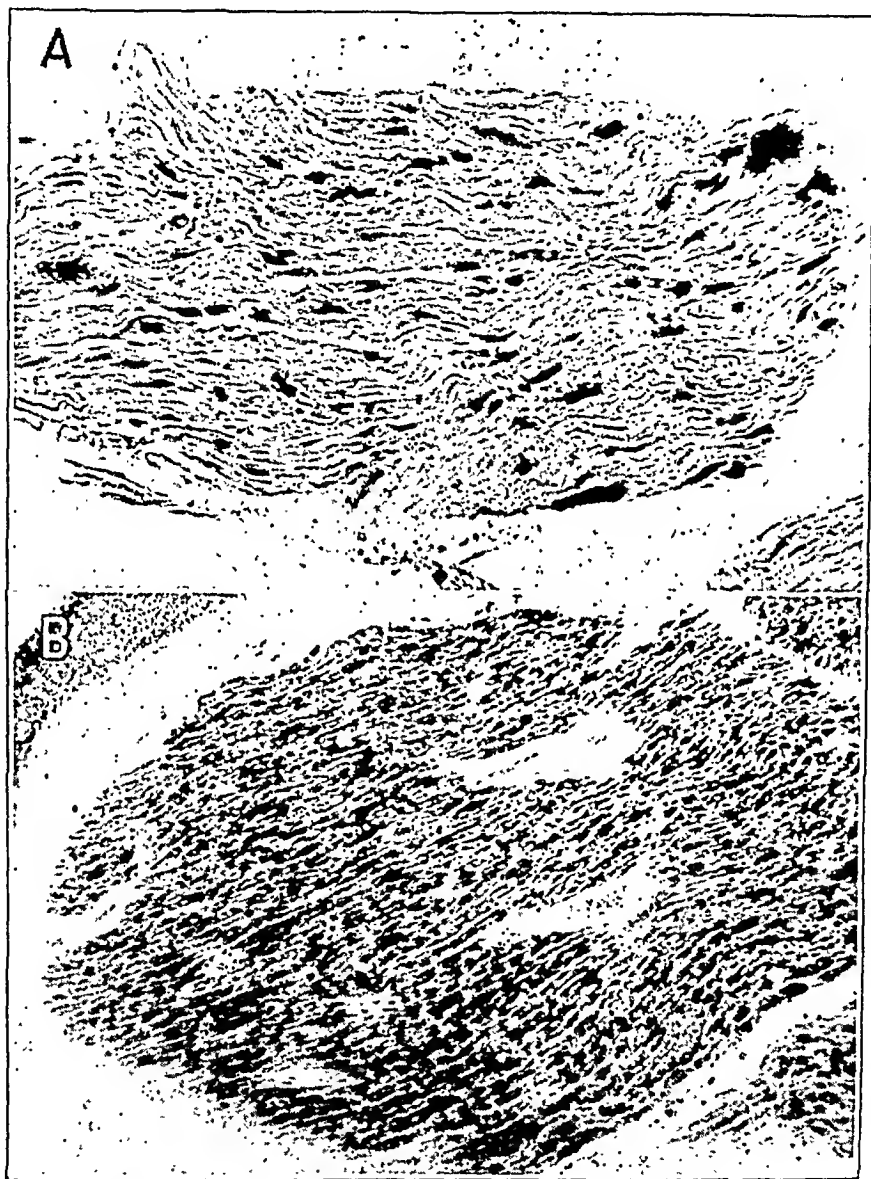


Fig. 2.—*A*, section of a posterior root from the cauda equina. The scattered black dots are the few remaining myelinated nerve fibers. Compare with *B*. *B*, section of an anterior root from the cauda equina, showing normal-appearing myelinated nerve fibers. Kultschitzky's stain for myelin sheaths; $\times 135$.

It is well to review the case reported here with regard to the establishment of the diagnosis of polyradiculoneuritis. While the criticism is not infrequently made that the diagnosis of polyradiculoneuritis is reached only after other diseases have been ruled out, there are certain constantly observed neurologic signs and symptoms which occur together frequently enough to justify the clinical concept

of a disease entity. The following clinical signs and symptoms observed in our case are generally regarded as characteristic of the disorder.

There was a severe and prostrating neurologic disease, which progressed from the initial symptoms, indicating only slight involvement of the sensory and motor systems, to complete quadriplegia with loss of vision. There was loss of facial expression on the left side of the face, indicating involvement of the seventh cranial nerve. The cerebrospinal fluid contained an increased amount of protein with a normal cell count (albuminocytologic dissociation). Recovery from the quadriplegia was rapid for three weeks, with greater improvement in the return of the motor than of the sensory functions, but after this initial period only slight improvement was noted. A history of infection of the respiratory tract or of another infectious disease, so frequently cited as a characteristic part of the syndrome of polyradiculoneuritis, was not obtained. The history of a preceding infectious disease is not as frequent as is generally inferred, however, for Fox and O'Connor⁵ found it present in only 31 per cent of the cases of polyradiculoneuritis reported in the literature.

We feel that syphilis can be excluded in our case, since all serologic studies, including those made on the spinal fluid during the most acute phase of the disease, gave negative reactions. There was no history of venereal infection or of anti-syphilitic treatment, and the clinical course of an acute neurologic disease with quadriplegia followed by improvement is certainly not characteristic of syphilis of the central nervous system. Furthermore, the pathologic examination of the nervous system revealed no evidence of an inflammatory disease.

A specific dietary deficiency as the cause of the disease seems equally unlikely, since the history obtained from the patient's family verified the statement made by him that his appetite was always good and his diet had been adequate. Furthermore, after entering the hospital he was immediately placed on a high vitamin diet; in spite of this, his most severe neurologic signs subsequently developed, and the synthetic vitamin preparations administered both orally and parenterally after their appearance had no manifest effect on the subsequent course of his disease.

The severe loss of myelinated nerve fibers in the posterior column, the dorsal roots and the peripheral nerves adequately explains the loss of deep tendon reflexes and position and vibration sensibility in the upper and lower extremities. The loss of motor power shown by the patient is difficult to explain anatomically, since there was no observable pathologic change in the anterior horns, the anterior horn cells or the anterior roots. The loss of motor function might be explained, however, as a purely functional loss resulting from the patient's long convalescence plus the functional impediment from the degeneration of the posterior column.

The pathologic observations gave additional support to the clinical diagnosis of polyradiculoneuritis because there was no evidence of inflammatory disease and the degeneration noted in the posterior column, accompanied by large numbers of gutter cells, was entirely in keeping with the clinical history indicative of acute degeneration there nineteen months before.

That the patient's previous neurologic disease was a contributing factor in the development of the intussusception which was the immediate cause of his death is impossible to say. If the autonomic nervous system was involved and damaged, its altered function might explain the occurrence of the intussusception. Unfortunately, this possibility was not thought of at the time of necropsy, and the autonomic nervous system was not examined. This possibility seems remote, however, since the patient showed no signs or symptoms indicating involvement of the autonomic nervous system, either during or after the acute phase of his neurologic disease.

5. Fox, M. J., and O'Connor, R. D.: Infectious Neuronitis: Review of Literature and Presentation of Four Cases, *Arch. Int. Med.* 69:58-66 (Jan.) 1942.

COMMENT

In the absence of a proved etiologic agent, polyradiculitis can be regarded only as a neurologic syndrome. It is conceivably possible, therefore, that this syndrome is not a single disease entity but merely a stereotyped reaction of the nervous system to one of several etiologic agents. For this reason sweeping generalizations about the disease should be avoided, and from the pathologic study of a single case we are reluctant to more than suggest that the pathologic changes we have noted are uniformly characteristic of the syndrome. There is, however, some basis for this suggestion.

In the case presented here, for example, the degeneration of the cells of the posterior root ganglia and the degeneration of the posterior column and peripheral nerves adequately account for the clinical signs and symptoms shown by the patient, which were regarded as typical of polyradiculoneuritis. Moreover, in the cases of polyradiculoneuritis reported in the literature⁵ loss of deep reflexes with sensory changes indicating involvement of the posterior column was nearly universally observed. Additional evidence that this disease primarily produces destruction of the posterior column of the spinal cord and the nerve fibers in the peripheral nervous system associated with it is obtained from study of the reported cases of polyradiculoneuritis in which there was residual neurologic disease. In all the cases in which details of the patient's convalescence were given the last neurologic sign to disappear was the loss of deep tendon reflexes and of position and vibration sense. Recovery from all loss of neurologic functions was usually complete in from six months to one year. Of a total of 130 cases of polyradiculoneuritis reported in the literature which we have reviewed, residual neurologic disease lasting over one year was recorded in 7 cases,⁶ and in every case there was either complete loss or moderate diminution of the deep reflexes. Sensory disturbances were occasionally noted, and in a few instances there was slight motor weakness. In 1 case, reported by Guillain,^{6b} the diagnosis of tabes dorsalis was made by a family physician five years after the attack of polyradiculoneuritis because of the absence of deep tendon reflexes and of position and vibration sensibility in the lower extremities. The exact nature of the patient's disease was subsequently revealed after the clinical history of an attack of polyradiculoneuritis was obtained and complete laboratory studies had revealed no serologic evidence of syphilis.

The pathologic changes in the nervous system noted in our case are in no way characteristic of any neurologic disease known to us. Syphilis can be completely eliminated as the cause since in the complete and thorough histologic examination of the nervous system no evidence of inflammatory disease was seen. The degeneration that was so strictly limited to the posterior column, the posterior roots and the peripheral sensory nerves does not resemble the pathologic changes in the nervous system described in deficiency diseases occurring in the human subject⁷ or in experimental animals.⁸ We did not observe the pathologic changes that Roseman and Aring³ and others have described in the ganglion cells and in the axis-cylinders in patients who died during the acute stage of the disease.

We were able to find but 1 other case of polyradiculoneuritis reported in the literature in which residual neurologic disease was present and pathologic studies

6. (a) Gilpin, Moersch and Kernohan,^{4c} cases 2 and 12. (b) Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid [cases 3 and 5], *Arch. Neurol. & Psychiat.* **36**:975-990 (Nov.) 1936. (c) McIntyre, H. B.: Infective Neuronitis [case 6], *Ohio State M. J.* **33**:815, 1937. (d) Roseman and Aring,³ cases 1 and 15.

7. Hsü, Y. K.: Pathologic Anatomy of Human Nervous System in Avitaminosis, *Arch. Neurol. & Psychiat.* **48**:271-319 (Aug.) 1942.

8. Swank, R. L.: Avian Thiamin Deficiency: A Correlation of the Pathology and Clinical Behavior, *J. Exper. Med.* **71**:683-702, 1940. Davison, C., and Stone, L.: Lesions of the Nervous System of the Rat in Vitamin B Deficiency, *Arch. Path.* **23**:207-223 (Feb.) 1937.

were made. This case, reported by Gilpin, Moersch and Kernohan,¹⁰ was not entirely comparable to the case reported here because the patient died of Hodgkin's disease only eight months after the onset of the polyradiculoneuritis. The authors expressed the belief that the neurologic disease was not in any way related to the Hodgkin's disease, although it was stated that the patient's neurologic symptoms were not entirely typical of polyradiculoneuritis. Furthermore, additional improvement in the lost neurologic functions could have been expected after eight months. Pathologic study of the nervous system disclosed loss of myelinated nerve fibers in the sciatic and femoral nerves and the brachial plexus without evidence of inflammation. The spinal ganglia showed but minimal change in the ganglion cells with a slight increase in the number of periganglionic cells. There was degeneration in the posterior column of the spinal cord with gliosis but no evidence of inflammatory reaction. The brain was not examined, and the clinical diagnosis of Hodgkin's disease was confirmed by the general pathologic examination. The pathologic changes in the nervous system described by Gilpin, Moersch and Kernohan¹⁰ in the case reported by them were remarkably similar to the changes in the case presented here. Although in the case described by these authors there was the complicating factor of Hodgkin's disease and the clinical course of the disease was admittedly not entirely typical of polyradiculoneuritis, the report only lends additional support to the general concept of this disease, namely, that it may be a stereotyped reaction of the central nervous system to one of several etiologic factors.

SUMMARY

A clinicopathologic study of a case of polyradiculoneuritis is reported. Recovery from the acute phase of the disease was followed by neurologic signs indicating degeneration of the posterior column of the spinal cord. The patient died nineteen months after the onset of his neurologic symptoms of an intussusception of the small intestine. Pathologic study of the nervous system disclosed loss of ganglion cells in the posterior root ganglia with degeneration of the posterior column of the spinal cord, the posterior nerve roots and the peripheral nerves, without inflammatory reaction. The observed pathologic changes were not regarded as characteristic of any known disease affecting the nervous system.

CONCLUSIONS

Polyradiculoneuritis is in rare instances followed by degeneration of the ganglion cells in the posterior root ganglia, the posterior column of the spinal cord and the peripheral nerves. It is suggested that polyradiculoneuritis may be a stereotyped reaction of the nervous system to one of several as yet unknown etiologic agents that produce the degeneration of posterior root ganglia, the posterior column of the spinal cord and the peripheral nerves.

Washington University School of Medicine.
City Sanitarium.

Clinical, Technical and Occasional Notes

MYASTHENIA GRAVIS

Familial Occurrence

HENRY ALSOP RILEY, M.D., AND MAURICE FROCHT, M.D., NEW YORK

The recording of these 2 cases calls attention to the possibility that myasthenia gravis may have a familial tendency. Reference to some of the standard textbooks on neurology discloses a difference of opinion as to a multiple familial occurrence. "Myasthenia gravis occasionally appears in more than one member of the family." (Bing¹); "There is never any familial or hereditary tendency in myasthenia gravis." (Ford²); "Heredity does not play any considerable role in spite of rare observations by Peter and Marina." (Curschmann³); "The disease is not familial or hereditary, but it appears to have a relationship to disease of the thyroid and the thymus glands, which have a tendency to run in families." (McCarthy⁴); "Heredo-familial tendencies are unknown save for the cases of Marinesco and Hart." (Wilson⁵); "The occasional presence of some heredo-degenerative stigmata naturally points to a congenital predisposition." (Wechsler⁶); "No case is on record in which more than one member of a family has been affected." (Campbell and Bramwell⁷).

Ever since the first description of this syndrome by Wilkes, in 1877, and by Erb and Goldflam, in 1878, its constitutional character has been emphasized by many authors. Oppenheim,⁸ in 1901, mentioned its association with a number of neurologic maldevelopments and diseases. Marinesco⁹ noted the condition in 2 sisters and postulated a hereditary tendency. In an elaborate review of the entire literature on this subject, Keschner and Strauss¹⁰ did not note its occurrence in several members in any one family but stated that "the striking developmental defects and deformities in the nervous system and in other organs found in many of these patients are believed by some authors to indicate that congenital predisposition plays an etiologic rôle." Hart¹¹ reported 2 cases in sisters and

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

1. Bing, R.: Textbook of Nervous Diseases, translated and enlarged by Webb Haymaker, St. Louis, C. V. Mosby Company, 1939, pp. 181-185.

2. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Baltimore, Md., Charles C Thomas, Publisher, 1937, p. 889.

3. Curschmann, H.: Myasthenia Gravis Pseudoparalytica, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 16, pp. 1005-1022.

4. McCarthy, D. J.: Myasthenia Gravis, in Osler, W.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1928, vol. 6, pp. 803-820.

5. Wilson, S. A. K.: Neurology, edited by A. Ninian Bruce, London, Edward Arnold & Co., 1940, vol. 2, p. 1596.

6. Wechsler, I.: Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1939, p. 209.

7. Campbell, H., and Bramwell, E.: Myasthenia Gravis, Brain **23**:277, 1900.

8. Oppenheim, H.: Die myasthenische Paralyse, Berlin, S. Karger, 1901; Zur myasthenischen Paralyse, Deutsche med. Wchnschr. **30**:1053, 1904.

9. Marinesco, G.: New Contribution to Pathogenesis of Myasthenia, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1369, 1925.

10. Keschner, M., and Strauss, I.: Myasthenia Gravis, Arch. Neurol. & Psychiat. **17**:337 (March) 1927.

11. Hart, H. H.: Myasthenia Gravis with Ophthalmoplegia and Constitutional Anomalies in Sisters, Arch. Neurol. & Psychiat. **18**:439 (Sept.) 1927.

stated that the familial occurrence of myasthenia is extremely rare. Rothbart¹² reported 4 cases of the disease in 4 brothers of a family. He treated 2 of these patients; a third who died in early infancy was reported to have had definite signs of myasthenia gravis, and in another brother lagophthalmos developed during an infection.

It would seem that although the familial occurrence of this syndrome is not common, its tendency to exhibit constitutional and familial features should not be forgotten.

REPORT OF CASES

CASE 1.¹³—Miss A. F., aged 26, a Jewess, born in Poland, was admitted to the New York Neurological Institute on April 8, 1942 with the chief complaint of fatigue and drooping of the eyelids.

History.—At the age of 11 years the patient first noticed the onset of fatigue and exhaustion. She could not play and run as well as other children. The symptoms have continued to progress up to the present. With the onset of menstruation, at the age of 12½ years, the symptoms of fatigue became so pronounced during the menses that she could scarcely comb her hair without becoming completely exhausted. She observed that her eyelids tended to droop when she was 11 years old, especially in the late afternoon, when she was most tired. The field of the fatigue gradually extended and involved walking, swallowing and talking. She was hardly able to swallow a glass of water, could not walk a block without stopping to rest and was unable to carry out any prolonged activity. When talking she was often forced to stop before she had finished because of the fatigue.

Since 1938 her symptoms have been so severe that she has been practically helpless. She has had pains all over her body—at times in the muscles, frequently in the knees. Since 1939 her eyelids have drooped practically continuously. She has never experienced any diplopia but has had pronounced limitation of ocular movements in all directions.

The patient stated that she felt mentally dull, torpid and “dopey” all the time, with no interest in anything; although she spent practically all her time in bed, rest no longer improved the condition of her muscles.

Personal History.—The patient had measles and whooping cough in infancy. Her general health was good until the age of 11. The menses were always irregular, occurring at intervals of twenty-one to twenty-eight days and lasting six days. Because of the irregular and prolonged menses and dysmenorrhea, she was operated on for uterine fibroids in 1938. This measure was followed by the menopause.

Her tonsils and adenoids were removed in 1937. She has had no accidents or injuries of any importance. She has had various gastrointestinal symptoms since 1941. At times she has had dyspnea on exertion, but she has never observed any edema of the ankles.

Family History.—There were 8 children in the family, 3 brothers and 4 other sisters, 1 of the latter being afflicted with the same disease that this patient presents. None of the other 6 children had any complaints resembling the condition presented by the 2 sisters reported on here. There was, however, a familial background of diabetes and hypertension.

Physical Examination.—The patient was pale and fatigued looking and was rather stout; she was 4 feet 10 inches (147 cm.) in height and weighed 133 pounds (60.3 Kg.). She had brown, coarse hair and a rather myasthenic facies. Elasticity of the skin was diminished. She had a moderate amount of hair over the lumbosacral region and patches of hair over the tibial crests. Only a few teeth were left, and some were carious. Her hands and feet were small. The thyroid was not enlarged. The mammae were rather large and pendulous, with a suggestion of chronic bilateral cystic mastitis. The blood pressure was 118 systolic and 72 diastolic. The pulse was regular in rate and rhythm. The heart was not enlarged. A systolic blow was present over the pulmonic area.

Neurologic Examination.—The patient was right handed. Her station was normal. She walked with a slow, stiff, hesitant, shuffling gait. She was unable to walk on her toes or heels or on a straight line. The muscles felt doughy and lacked the usual tonicity. The patient insisted she could not stand on one leg because she was tired. Her speech, although distinct at first, became nasal, slow and slurring after the utterance of a few sentences,

12. Rothbart, H. B.: Myasthenia Gravis in Children, J. A. M. A. **108**:715 (Feb. 27) 1937.

13. An earlier report of this case was made by N. W. Winkelman and M. T. Moore (Prostigmin in the Treatment of Myasthenia Gravis and Muscular Dystrophy, Arch. Neurol. & Psychiat. **37**:237-252 [Feb.] 1937).

separate words becoming scarcely recognizable. The nasolabial folds were almost obliterated. Examination of the cerebral nerves showed the following changes: There were bilateral ptosis and right internal strabismus. She could not move the right eye outward. Upward movement was impaired in both eyes, but downward movements and convergence were fairly well maintained. Repetition of these movements resulted in rapid fatigue. The pupils were equal and reacted to light and in accommodation. There was a moderate degree of retinal arteriosclerosis. The facial musculature showed little play as a result of internal or external stimuli. She could move the frontalis muscle, but continued movements resulted in rapid exhaustion of this muscle. The strength of the masseter muscles was normal. The functions of the remaining cerebral nerves were normal except for fatigue of the uvula on repeated elevation.

Laboratory Data.—The blood was normal except for slight anisocytosis and occasional polychromatophilia. The erythrocyte sedimentation rate was 12 mm. in one hour. The serum cholesterol measured 240 mg. per hundred cubic centimeters. The blood sugar was 103 mg. per hundred cubic centimeters. The creatinine excretion was 792 mg. in twenty-four hours and the creatine excretion was zero. The basal metabolic rate was —15 per cent.

Roentgenographic Examination.—The skull was normal. Roentgenograms of the chest revealed nothing abnormal except for scoliosis in the upper dorsal region. Lateral and oblique views showed no evidence of a mediastinal tumor.



Ptosis, the result of pronounced fatigue following movements of the frontalis muscle and opening and closing of the eyes for twenty seconds.

Electrical Examination.—The Jolly reaction was slightly positive in the abductor minimi digiti and the extensor digitorum communis muscle. Values for chronaxia were within the normal range. After faradization of the frontalis muscle, there was an increase in chronaxia to about twice the normal value, which was consistent with the diagnosis of myasthenia gravis.

Mental Status.—The intelligence quotient was 65.

Medication.—The patient had received various types of medication. Ephedrine at first helped her a great deal, but she has obtained no benefit from its use since 1939. She has also been given prostigmine. Prior to the operation in 1938 the drug was effective, but since then it has been ineffectual. Administration of the drug did not improve the defects in the lateral gaze but did increase the movements of the eyelids.

CASE 2.—Mrs. S. O., aged 38, married, a sister of A. F. (case 1), was also admitted to the Neurological Institute on April 8, 1942, with the chief complaint of diplopia, fatigue and drooping of the eyelids.

History of Illness.—Fatigue had been present since the age of 14 years and drooping of the eyelids since the age of 8 years. At the age of 14 years the patient noticed that she became more fatigued than the other children with whom she played, and this tendency grew worse over a period of years. In 1938 the fatigue and exhaustion became extreme.

Her extremities felt like lead. Any activity, such as combing her hair or walking even a block, could scarcely be completed because of the rapidly induced ingravescent fatigue. She noticed that when she talked she could not finish what she was saying because she became so tired. Swallowing had become progressively difficult, until she could scarcely complete the drinking of a glass of water before tiring. She could, however, eat solid food, but chewing became difficult long before the end of an average meal. The fatigue formerly passed off after she had rested for a while, but since 1938 she had been tired all the time. She felt that from 1938 until 1940, that is, after her hysterectomy, she was much better than before. She was more energetic, could walk better and could take care of herself without any difficulty. She could swallow, talk and eat as well as other people, but in 1940 the severity of the previous symptoms, which had almost incapacitated her in 1938, recurred with greater intensity than before. The progressive severity of these symptoms has continued up to the present.

The patient's mother noticed that at about the age of 8 years the child's eyelids seemed to droop. This persisted until the age of 23, when an operation was performed to raise the lids. This measure gave relief for six months, when the lids again drooped. At present, when she is tired, her eyelids close despite any effort to keep them open. Diplopia is present whenever she is fatigued.

Since the age of 14 the patient has noticed limitation of movements of her eyes in all directions and has had to turn her head to see objects on either side.

All the aforementioned symptoms formerly were absent in the morning, after a night's rest. However, during the past few years these symptoms have become aggravated and have been present practically constantly, even after a night's rest. She has noticed that she perspires a great deal, frightens easily and has become dull, torpid and without interest in anything. She spends most of her time in bed.

Personal History.—The patient sleeps normally. She began to wear glasses seventeen years ago. Her periods began at the age of 17, occurring every twenty-one days and lasting about six days. Because of irregular menses and profuse bleeding, a hysterectomy was performed in 1938. In 1940 she had symptoms suggesting a menopausal syndrome, with hot flushes, nervousness and shooting pains. She had occasional nocturia, and on rare occasions frequency of urination. She has never been pregnant. She is constipated.

Physical Examination.—The patient was moderately well developed, weighed 125 pounds (56.7 Kg.) and was 4 feet 11 inches (149.8 cm.) tall. She was pale and sallow, with a wrinkled skin, and was moderately obese. The thyroid was not palpable. The mammae were large and pendulous. The pulse was regular in rate and rhythm. The heart was not enlarged, and the heart sounds were of good quality, but the aortic second sound was greater than the pulmonic second sound and was bell-like in quality. The blood pressure is 150 systolic and 90 diastolic.

Neurologic Examination.—The patient was right handed. Her station was normal. She walked with a slow, awkward, stiff gait. She was unable to walk on her heels or toes or on a straight line. The muscles were generally flabby, and the muscles of the thigh felt doughy. She was unable to stand on one leg because of weakness. She talked with a slight nasal twang, and her voice fatigued readily. Speech was slurred and bulbar in type. In contrast to her sister's, her face was full of expression, although there was bilateral ptosis and the eyebrows were held in an arched position. The nasolabial folds were well outlined. All the deep reflexes were active and within normal limits. The abdominal reactions were present, and the plantar response was normal. The sensory status was normal for all modalities. The cerebral nerves showed the following changes: There were bilateral ptosis and limitation of ocular movements in the lateral direction. Upward movements were also limited in both eyes, but convergence was fairly well performed. High grade myopia was present. The pupils were even and reacted to light and in accommodation. The fundi were well visualized, and there was a moderate degree of retinal arteriosclerosis. She was able to move the frontalis muscle well, but repetition of these movements resulted in rapid fatigue. The strength of the masseter muscles was normal. The functions of the remaining cerebral nerves were normal.

Laboratory Data.—The blood count was normal except for slight anisocytosis. The serum cholesterol measured 278 mg. per hundred cubic centimeters. The creatine excretion rate was 32 mg. and the creatinine excretion rate 606 mg. in twenty-four hours. The basal metabolic rate was —20 per cent.

There was no evidence of enlargement of the spleen. The skull was normal.

Electrical Examination.—The muscles of the face did not show any fatigue reaction or any increase of chronaxia after fatigue. The Jolly reaction was slightly positive in the extensor digitorum communis muscle.

Mental Status.—The intelligence quotient was 76.

Medication.—This patient, like her sister, benefited little from any form of medication. She has been to numerous physicians and has had many kinds of medication. Until approximately a year ago, ephedrine roused her from her torpor and exhaustion, but for the past year or year and a half, this drug has had no effect whatever. However, neither of the sisters had ever been given systematic treatment with prostigmine. Prostigmine methylsulfate was given in the usual dose for diagnostic confirmation, and both patients responded satisfactorily.

SUMMARY

The 2 cases of myasthenia gravis, occurring in sisters, presented here fulfil satisfactorily the requirements for the diagnosis of this syndrome.

1. The onset of the disease was characterized by weakness of striated muscles and involvement of the ocular and bulbar muscles.

2. Abnormal and unusual fatigue was the outstanding feature in each case. This was demonstrated repeatedly.

3. A history of remissions and exacerbations was present in each case.

4. The myasthenic reaction of Jolly was definitely positive in 1 case and mildly positive in the other.

5. Both the patients had low intelligence quotients.

6. Temporary improvement, even though of short duration, followed the injection of prostigmine methylsulfate in both cases.

7. The familial background was one of diabetes, hypertension and cardiac disease.

These 2 cases of myasthenia gravis constitute the fourth instance reported in medical literature in which more than one member of a family was involved. It is believed that a more careful search and a complete history in each case of myasthenia may reveal additional data concerning a tendency of this disease to develop in more than a single member of a family.

The chronaxia tests were performed by Dr. Joseph Moldaver, and the psychometric examinations, by Miss Gladys Tallman.

117 East Seventy-Second Street.

610 West One Hundred and Tenth Street.

News and Comment

SYMPOSIUM ON MILITARY PSYCHIATRY

The Michigan Society of Neurology and Psychiatry devoted its meeting of March 25, 1943 to a round table discussion on the subject "The Importance of Neuropsychiatry in the Selection of Men for the Armed Forces." Dr. John M. Dorsey, president of the society, presided at the meeting, and Dr. Thomas J. Heldt, physician-in-charge of the Division of Neuropsychiatry at the Henry Ford Hospital, Detroit, acted as moderator. The speakers included Col. Leonard G. Rowntree, Medical Corps, Army of the United States, Medical Director of the Selective Service System; Brig. Gen. LeRoy Pearson, Medical Corps, Army of the United States, Director of the Selective Service System for the State of Michigan; Lieut. Col. William C. Menninger, Medical Corps, Army of the United States, Neuropsychiatric Consultant to the Fourth Service Command, Medical Branch, Atlanta, Ga.; Commander Francis J. Braceland (MC), U. S. N. R., National Naval Medical Center, Bethesda, Md.; Major Clarence I. Owen, Medical Corps, Army of the United States, State Medical Officer, Selective Service System for the State of Michigan, and Lieut. Col. Roscoe W. Cavell, Medical Corps, Army of the United States, Senior Medical Officer, Detroit Army Induction Station, Detroit.

The purpose of the symposium was to bring together representatives of the Selective Service System and the armed forces in order to promote a better mutual understanding of the neuropsychiatric problems which occur in the selection of men for the armed forces and in order to emphasize the need for recognition of potential neuropsychiatric casualties. The meeting was open to physicians and officers of the local draft boards.

THE AMERICAN PSYCHIATRIC ASSOCIATION

At the ninety-ninth annual meeting of the American Psychiatric Association in Detroit, May 10 to 13, 1943, the following officers were elected: president, Edward A. Strecker, M.D., Philadelphia; president-elect, Karl M. Bowman, M.D., San Francisco; secretary-treasurer, Winfred Overholser, M.D., Washington, D. C.; auditor, Ralph C. Hamill, M.D., Chicago; councillors, Thomas A. Ratliff, M.D., Cincinnati; Arthur H. Ruggles, M.D., Providence, R. I.; Raymond W. Waggoner, M.D., Ann Arbor, Mich., and G. Alexander Young, M.D., Omaha.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

STUDIES OF LIVING NERVES: VII. GROWTH ADJUSTMENTS OF CUTANEOUS TERMINAL ARBORIZATIONS. CARL CASKEY SPEIDEL, *J. Comp. Neurol.* **76:57** (Feb.) 1942.

Speidel studied in living tadpoles the changes in cutaneous nerve endings during growth from shortly after hatching until the fully grown stage. He found that individual endings of the same fiber independently may undergo either extension or retraction, that new branches may arise and grow out and that old branches may be entirely eliminated by either retraction or degeneration. Degeneration was sometimes preceded by autotomy. During a period of twenty-six days, 38 endings developed on a terminal arborization, and 13 were eliminated. The longest ending was 200 to 250 microns. In a forty-eight hour period the extension was usually less than 100 microns and the retraction less than 50 microns. The shape of the terminal swelling varied according to the activity of the arborization. Shifts in position of a nerve ending tip were brought about by growth or retraction, by retraction followed by growth in a new direction, by development of a new branch followed by loss of the old tip and by degeneration of a variable length near the tip with or without preceding autotomy. Aberrant endings located deeply sometimes underwent adjustment to reach the surface.

FRASER, Philadelphia.

EXPERIMENTAL VERIFICATION OF THE DIFFERENCES IN THE ARGYROPHILIA OF SYMPATHETIC POSTGANGLIONICS AND OF OTHER NERVE FIBERS. JOSÉ F. NONIDEZ and KENDRICK HARE, *J. Comp. Neurol.* **76:91** (Feb.) 1942.

In order to verify that the pale fibers in the cardiac nerves are sympathetic postganglionic fibers, Nonidez and Hare excised the ventral roots and dorsal root ganglia from the first to the sixth thoracic segment unilaterally in 2 puppies. A week later the vagosympathetic trunk in the neck and the sympathetic chain at the level of the fifth rib were cut. The animals were killed eight and thirteen days later. The sympathetic chains from each side were prepared with silver. Some regeneration of preganglionic roots had occurred in both animals. The ganglia which had been operated on showed (1) absence of the intercellular plexus formed by the terminal branches of the preganglionic fibers; (2) only a small number of deeply stained fibers, which were preganglionic fibers either degenerating slowly or undergoing regeneration, and (3) intact postganglionic fibers all lightly impregnated. Nonidez and Hare suggest that the differential argyrophilia is probably due to chemical differences in the protoplasm of the neurons.

ADDISON, Philadelphia.

THE TOPICAL ORGANIZATION AND TERMINATION OF THE FIBERS OF THE POSTERIOR COLUMNS IN MACACA MULATTA. A. EARL WALKER and THOMAS A. WEAVER JR., *J. Comp. Neurol.* **76:145** (Feb.) 1942.

Walker and Weaver sectioned the posterior roots in 8 macaque monkeys; in 16 animals chordotomy or myelotomy was performed. In these operations the posterior columns were sufficiently injured to give a reaction with the Marchi technic. In general, the ascending fibers are displaced medially and dorsally by more proximal incoming fibers. The fibers of the sacral roots ascend in the posterior column along the midline and in the dorsomedial angle of the funiculus, ending in the caudal and medial portion of the nucleus gracilis. The fibers of the lumbar roots pass rostrally in the middle of the fasciculus gracilis and terminate in the nucleus gracilis slightly oral and lateral to those from the sacral roots. As the fibers from lower segments ascend in the posterior column, many pass into the posterior horn and end there, so that less than half of the sacral fibers observed in the lumbar region are present in the cervical region. The fibers from the lower thoracic roots traverse the lateral portion of the fasciculus gracilis and end in the oral and lateral parts of the nucleus gracilis. The fibers from the upper thoracic roots ascend in the medial part of the fasciculus cuneatus and terminate

in the medial parts of the nucleus cuneatus proprius and nucleus cuneatus externus. The fibers from the cervical roots lie in the lateral portion of the cuneate fasciculus and terminate laterally in the cuneate nucleus.

FRASER, Philadelphia.

THE DEVELOPMENT OF LATE GASTRULA ECTODERM IN REGENERATING TISSUE OF *RANA PIPPIENS* LARVAE. HENRY S. EMERSON, J. Exper. Zool. **90**:353 (Aug.) 1942.

Late gastrula ectoderm in the blastema forms atypical brains, eyes with lenses and cartilage. It also forms definitive epidermis, suckers, horny jaws and teeth and nasal sacs. Brain, eyes and cartilage are confined to the presumptive neural plate, while presumptive epidermis forms only definitive epidermis and epidermal derivatives. The latter ectoderm curls up into a vesicle with the outer ectodermal surface inside, but the organs of the central nervous system develop directly from the ectoderm without forming a vesicle. Since nasal sacs without any nerve tissue, as well as horny teeth and jaws, come from gastrula ectoderm taken from the large yolk plug stage, there is good evidence that the normal development of these organs is induced by the roof of the archenteron, and not by the forebrain. Nearly all of the ectodermal surface of the late gastrula can form suckers in the blastema. Since the morphogenesis and histogenesis of the graft derivatives are nearly normal, the mesenchyme of the blastema is a favorable environment for the development of embryonic tissues and organs.

WYMAN, Boston.

THE NERVOUS SYSTEM AND REGENERATION OF THE FORELIMB OF ADULT *TRITURUS*: I. THE ROLE OF THE SYMPATHETICS. MARCUS SINGER, J. Exper. Zool. **90**:377 (Aug.) 1942.

Removal of the somatic supply to the forelimb (*Triturus viridescens*) by extirpation of the third and fourth or of the third, fourth and fifth spinal ganglia without damage to the sympathetic nerve supply was not followed by regeneration except in a few animals. The regeneration could be explained on the basis of somatic fibers. After unilateral sympathectomy of the cord typical regeneration occurred. It is concluded that the normal sympathetic supply is not essential for regeneration, whereas the somatic supply in part is required.

WYMAN, Boston.

TRANSPLANTATION OF ANEUROGENIC FORELIMBS IN *AMBLYSTOMA PUNCTATUM*. JEAN PIATT, J. Exper. Zool. **91**:79 (Oct.) 1942.

Forelimbs made aneurogenic by extirpation of segments of the spinal cord at stages 23 to 25 were allowed to develop until ten to fourteen days after feeding (parabiosed to a normal mate) and then were grafted in place of the right forelimb of a normal larva. Normal function of the grafted forelimbs occurred as early as fifteen days after transplantation. The nerve pattern formed by the brachial nerves of the host was almost normal in the majority of limbs and was never chaotic. The innervation of specific muscles was within the limits of normality. Prior to transplantation none of the limbs showed any motor or sensory activity, and histologic examination of the donor animals revealed that there was no possibility of innervation in 19 of these animals. Piatt concludes that nerves can form almost normal distribution pathways within an organ the histogenesis and morphogenesis of which have been completed prior to nerve invasion and the tissues of which are devoid of degenerating nerves. The role of the nerve fiber in attaining its peripheral distribution may not be entirely passive.

WYMAN, Boston.

Physiology and Biochemistry

STUDIES ON THE METABOLISM OF BRAIN SUSPENSIONS: I. OXYGEN UPTAKE. K. A. ELLIOTT and B. LIBET, J. Biol. Chem. **143**:227, 1942.

Suspensions of brain tissue, prepared by homogenization in mediums made isotonic with salts, sucrose or dextrose, respire up to 400 per cent faster than suspensions prepared in hypotonic mediums. An isotonic solution of urea behaves like a hypotonic medium. Addition of salt or sucrose to a suspension homogenized in a hypotonic medium causes increases up to 65 per cent in the respiratory rate. The initial respiration of dextrose-containing isotonic brain suspensions in sodium chloride is considerably decreased by small amounts of Ca^{++} or

Mg,⁺⁺ but these ions improve the maintenance of activity. The magnesium ion has little effect in the absence of dextrose or in hypotonic suspensions. The presence or absence of bicarbonate has no effect. Sodium chloride, sodium sulfate and sodium phosphate have specific stimulating effects. The potassium ion is inhibitory. Suspensions respire initially at the same rate in air as in oxygen. After an hour the respiration is progressively inhibited by oxygen. Oxygen inhibition can also be shown with slices of cortex. Dilution of isotonic suspensions with isotonic medium has little effect on the activity per unit weight of tissue. The activity of hypotonic suspensions decreases somewhat on dilution.

Homogenization in a hypotonic medium causes brain largely to lose the power of oxidizing dextrose. Small additions of citrate to dextrose-containing isotonic suspensions cause increases in the initial respiratory rate, which are dependent on the presence of magnesium. With or without magnesium, citrate improves the maintenance of the rate. In the absence of dextrose and in hypotonic suspensions citrate has no effect or inhibits slightly. Malate causes an initial acceleration of respiration, followed by some inhibition, in the presence or absence of dextrose and magnesium; its accelerating effect is larger with hypotonic suspensions. Fumarate slightly accelerates the initial respiration of isotonic suspensions and causes improved maintenance of rate. With hypotonic suspensions fumarate causes considerable initial acceleration, but less than malate, and inhibition does not set in. Heated liver extract causes considerable initial increase in respiration, especially with hypotonic suspensions, followed by inhibition. Insulin has no effect. Metrazol in relatively high concentration inhibits respiration.

The respiratory activity of slices of cortex and that of suspensions of whole brain are compared. The authors show that slices and suspensions behave in most respects in the same way but that isotonic suspensions are possibly more suitable, and certainly more useful, preparations for studies of brain metabolism.

PAGE, Indianapolis.

HISTOCHEMICAL CHANGES ASSOCIATED WITH AGING: II. SKELETAL AND CARDIAC MUSCLE IN THE RAT. O. H. LOWRY, A. B. HASTINGS, T. Z. HULL and A. N. BROWN, *J. Biol. Chem.* **143**:271, 1942.

The concentrations of water and chloride in the skeletal muscle of the rat decrease during growth and rise again in old age. The concentrations of potassium and phosphorus likewise decrease during growth but continue to fall in senescence. The changes in cardiac muscle are similar but much less pronounced. Considerable variation exists in the extent of the chemical changes in the muscle of the oldest animals. When these changes are interpreted histochemically, there appears to be an increase during growth in the proportion of intracellular tissue at the expense of the extracellular compartment. In the middle period of life little change is observed; but in senescence the relative mass of the intracellular compartment decreases, particularly in skeletal muscle, leaving a greatly increased extracellular compartment. In the adult the proportion of extracellular material is much greater in cardiac than in skeletal muscle and the increase with age is much less extensive.

These changes in the relative amounts of the major tissue compartments may have important consequences: (a) The increase in the amount of extracellular fluid in skeletal muscle in old age may affect the efficiency of exchange between blood and fibers; (b) the variation during life in the proportion of fibers in a given weight of muscle may explain some of the changes occurring in the metabolic activity and mechanical ability of muscle at different ages. During senescence no evidence was found for desiccation of the whole muscle, the extracellular portion of tissue or the fibers. The changes in the water and solids of the extracellular compartment of cardiac and skeletal muscle during aging were slight. The concentration of collagen in the extracellular compartment was not increased in old age. The intracellular concentrations of phosphorus and potassium decreased during growth in skeletal muscle, but during senescence the concentrations of water, total phosphorus and potassium in the muscle fibers underwent no significant change. Similarly, senescence produced no definite change in the water and total phosphorus concentrations in the cardiac muscle fibers.

PAGE, Indianapolis.

Psychiatry and Psychopathology

THE NEUROMUSCULAR HYPERTENSION AND THE UNDERSTANDING OF NERVOUS CONDITIONS. TRYGVE BRAATÖY, *J. Nerv. & Ment. Dis.* **95**:550 (May) 1942.

Pain and fatigue are symptoms caused by a multitude of factors, some of them so obscure that even painstaking clinical investigation fails to explain them. Under this category fall the complaints of many patients usually designated as neurotic, although the author points out

that all healthy persons have at times suffered from ill defined and poorly localized sensations of pain and tiredness in a limb. These feelings actually originate within the muscles; hence it is of great importance for the physician to be able to test the state of muscular tension or relaxation and for the patient to become aware of it. In educating the patient to awareness of his muscle sense, a careful course of training must be instituted. Considerable individual variation is found, and there is difficulty in making the patient distinguish between contraction of single muscles and movements of a part.

Braatöy believes that muscular overstrain, or, as he calls it, hypertension, is frequently the starting point for neurotic symptoms. Sometimes the actual mechanism of "repressing an emotion" lies in contracting the maxillary, respiratory and abdominal muscles, and the maintenance of some degree of contraction over a long period may cause pains due to muscular hypertension. A natural accompaniment is the sensation of fatigue.

Such more or less fixed hypertension of the respiratory and abdominal muscles leads to an interest in the behavior of respiration in neurotic persons, which shows that there is practically always failure to relax the muscles, with consequent costal breathing. Because of the reflex relationship between muscular tonus and vegetative functions, relaxation in the breathing habits of a patient often leads to improvement in other systems, such as the vascular and the gastrointestinal apparatus.

One result of the author's muscle sense training in 2 cases was the eliciting from the patients of material of anamnestic value, brought out by specific findings referred to the muscular system. Also, the differential investigation of muscle sense, especially with regard to asymmetries, may provide a clue to the existence of neurologic abnormalities.

CHODOFF, Langley Field, Va.

REPORT OF A FAMILY EXHIBITING HEREDITARY MIRROR MOVEMENTS AND SCHIZOPHRENIA.
BERNARD C. MEYER, *J. Nerv. & Ment. Dis.* **96**:138 (Aug.) 1942.

Meyer discusses the occurrence in various members of the same family group of schizophrenia and pathologic synkinetic phenomena. Since a possible etiologic relationship between the two conditions was suggested, a complete family pedigree was prepared in order to investigate the hereditary aspects of the problem. Hereditary synkinesia has been shown to be transmitted as a single dominant factor, and the occurrence of the disorder in the family studied followed such a pattern. In accordance with Kallman's investigations, schizophrenia was considered to be based on a single recessive genetic factor, and the number of cases of schizophrenia, schizoid personality and schizoid psychopathy found on both sides of the family was entirely consistent with the expectations to be fulfilled in accordance with this belief. Meyer concludes that the two conditions are completely independent of each other from the genetic view, each factor following its own line of inheritance.

Mirror movements have been described in persons with hemiplegia and hemiparkinsonism and as a physiologically healthy activity in infants and young children. In pathologic cases, the lesion responsible for the condition has been placed by various authors in the substantia nigra, the spinal cord and a hypothesized inhibitory center in the parietal lobe. Meyer believes that none of the suggested sites of origin can explain all the clinical cases and suggests instead that the syndrome is due to a break anywhere in a long conduction pathway close to, but not identical with, the pyramidal tract. The movements would then be regarded as a release phenomenon similar in nature to the hyperactive reflexes of disease of the pyramidal tract. Mirror movements initiated by passive motion are attributed to an identical mechanism except that here the movement is the effector end of a reflex arc initiated by a proprioceptive stimulus.

CHODOFF, Langley Field, Va.

VISUAL HALLUCINATION DURING PARALDEHYDE ADDICTION. MARCEL HEIMAN, *J. Nerv. & Ment. Dis.* **96**:251 (Sept.) 1942.

Addiction to paraldehyde in some cases causes rather characteristic visual hallucinations, especially during withdrawal periods and usually as part of a delirious state. Heiman reports the case of a paraldehyde addict who frequently had a visual hallucination in the form of a symmetric fernlike net, which under certain conditions gave the illusion of movement. The pattern of the hallucination resembled closely the type of "form constants" described as seen under the influence of mescaline. The phenomenon was perceived only under conditions of indistinct lighting and incomplete adaptation. The unvarying nature of the hallucination each

time it appeared suggested comparison with the visual aura preceding an epileptic seizure. The pattern of the phenomenon was probably determined by the fact that the patient was looking at a plant composed almost entirely of stems and stalks just before its first appearance. Thus, like a visual aura, the experience seemed to consist mainly of a forced repetition and a rigid after-effect. Its physiologic substrate appeared to depend on a state of increased irritability of a cortical area during the patient's withdrawal period. The phenomenon, when present, filled the entire visual field, and its appearance was accompanied by inability of the patient to orient himself in space. The apparent movement of the phenomenon was related to the patient's own movements and is explained on the basis of disturbance of spatial stability, which is ordinarily maintained by harmonizing forces belonging to the vestibular and the optosensory apparatus.

CIBODOFF, Langley Field, Va.

MICROPSIA. LEO H. BARTEMEIER, *Psychoanalyt. Quart.* 10:573, 1941.

Hysterical micropsia differs from that of organic origin in that the object appears to recede as it becomes smaller and there is microscopic vision even when the lids are closed. In Bartemeier's patient, a married woman aged 28, the micropsia was a conversion symptom expressing a wish that the object toward whom the patient had hostile feelings, might be removed and thus destroyed so that the patient could not harm it. The symptom followed the birth of a younger brother, which made the patient intensely ashamed of her mother and angry at her father and the baby. The path to the use of the eyes for the purpose of expressing hostility lay through the childhood experience that when the patient was angry at her mother she made faces and crossed her eyes. This induced the mother to warn her that this practice would hurt her eyes. As in the cases reported by Inman, the aggression was oral and originated in a prolonged nursing period and subsequent inability to express fully her intense aggression.

PEARSON, Philadelphia.

MYASTHENIA GRAVIS AND PSYCHOSIS. M. HAYMAN, *Psychosom. Med.* 3:120 (April) 1941.

Hyman describes a case of myasthenia gravis in which, two years after the onset of the illness, there developed a psychiatric disorder characterized by depression and delusions of persecution and of grandeur. These delusions were colored by the somatic symptoms of the patient. As was to be expected, the emotional upheaval of rage which occurred on the slightest provocation resulted in severe respiratory embarrassment. The author speculates concerning the possibility of a more or less specific reciprocal relationship between the somatic and the psychic manifestations which were present in this case of myasthenia.

SCHLEZINGER, Philadelphia.

THE INCIDENCE OF NEUROSIS IN CASES OF BRONCHIAL ASTHMA. V. SCHATIA, *Psychosom. Med.* 3:157 (April) 1941.

Schatia studied a series of 40 cases of bronchial asthma by means of the Rorschach test in an effort to determine the incidence and character of the neurosis. The interpretation of the composite Rorschach record in this series apparently indicates that asthmatic patients have psychoneuroses of the obsessional type. Their personalities are characterized by a tendency to rigidity in their reactions, with covering of emotional turmoil by excessive intellectualization.

SCHLEZINGER, Philadelphia.

THE EMOTIONAL SETTINGS OF SOME ATTACKS OF URTICARIA. L. J. SAUL and C. BERNSTEIN JR., *Psychosom. Med.* 3:349 (Oct.) 1941

Saul and Bernstein consider the problem of urticaria as a psychosomatic manifestation through a detailed investigation of a single case. They focus their attention not on the details of the patient's personality structure but on the emotional states occurring at the time of the urticarial attacks. The subject for study was a young woman with intense longings for love who was unable to satisfy these desires by normal sexual relationship with a man because of her fears and inhibitions. Urticaria developed at times when her desires were especially stimulated and frustrated. Twelve urticarial episodes were observed during the analysis, and their emotional settings are described. Eight of them occurred in connection with dreams which ended always on the verge of frustration in a situation in which a desire was portrayed

as almost but not quite satisfied. Other types of dreams were never followed by urticaria. However, a repetitive dream in which a reached-for object or person slipped from the patient's grasp was sometimes followed by weeping instead of by urticaria. The urticaria appeared when weeping was repressed and often ceased when the patient cried. The findings were confirmed by the analysis of a second patient and by a few observations on 5 patients who were examined in interviews. On the basis of these results, as well as other observations in cases of asthma, Saul and Bernstein suggest the possibility that there may be a relationship between certain states of allergic sensitivity and psychodynamic states of intense frustrated longings.

SCHLEZINGER, Philadelphia.

BLOOD PRESSURE AND PULSE CHANGES IN NORMAL INDIVIDUALS UNDER EMOTIONAL STRESS: THEIR RELATIONSHIP TO EMOTIONAL INSTABILITY. D. P. MORRIS, *Psychosom. Med.* 3:389 (Oct.) 1941.

Morris utilized a group of 62 student nurses between 18 and 25 years of age and a group of 17 student pilots between 19 and 25 years of age in an effort to determine whether there was any correlation between emotional instability and blood pressure or changes in pulse rate in normal persons subjected to emotional stress. The blood pressures and pulse rates of the student nurses were obtained at their initial physical examination, which was considered by the author to be an experience characterized by considerable emotional stress. Similarly, the blood pressures and pulse rates of the student pilots were obtained at the time of the qualifying physical examination, but they were also studied at the time of the initial flight, and in a few cases just before the initial attempt to perform a difficult aeronautic maneuver. Relatively superficial psychiatric surveys were made of the subjects in both groups. From the data obtained, it is concluded that elevations of the systolic blood pressure of 10 to 30 per cent above the basal level in situations of mild emotional stress are not abnormal. It was further noted that there was no correlation between these elevations in blood pressure and the incidence of cardiovascular disease in the family. The changes in pulse rate were more variable than the blood pressure and included both increases of 40 per cent and decreases of 20 per cent. The author concludes that vascular reactions to emotional stress such as were obtained in the nurses and student pilots are so common that they can be considered a normal physiologic response.

SCHLEZINGER, Philadelphia.

BRAIN POTENTIALS AND MORPHINE ADDICTION. H. L. ANDREWS, *Psychosom. Med.* 3:399 (Oct.) 1941.

Andrews studied the electroencephalograms of a series of 50 men during a period of maintained addiction to morphine, as well as the records of another series of 50 men in whom addiction to morphine had been terminated for at least one year. It was observed in both groups that the distribution curves for the percentage of alpha activity did not conform with the electroencephalographic patterns described for normal subjects. The records of men during maintained addiction to morphine were characterized by an abnormally high percentage of alpha activity associated with a lowered alpha frequency. In some instances the high alpha index was maintained after withdrawal of morphine, while in others there was a sharp drop. Of particular significance was the fact that a high percentage of alpha activity was maintained during the active phase of withdrawal in spite of a high degree of emotional tension, which in normal subjects usually abolishes the alpha rhythm. Because of the comparatively slight effects of withdrawal of the drug on the electroencephalogram, the author infers that the primary reaction of morphine is not on the cortex or the corticothalamic system but rather on the hypothalamus.

In general a single dose of morphine had no appreciable effect on the brain potential record of a nonaddict. However, for 1 patient a characteristic sleeping rhythm was recorded when he was not asleep.

SCHLEZINGER, Philadelphia.

MILITARY PSYCHIATRY. WILLIAM C. PORTER, *War Med.* 2:543, 1942.

Porter raises a number of interesting questions in relation to psychiatric problems among the armed forces. He points out that the rejection of an inductee for psychiatric reasons may work the inductee harm on return to his community. He suggests that instead of certifying a man as rejected for psychiatric reasons, it would be better to state that the inductee is not

suited for military service because of personality defects but is suited or unsuited for selected civilian war work. He asks the question whether present psychiatric knowledge is sufficient to make certain that the men they reject are really unsuited for military service and cites a number of examples of men who seemed unsuited but made excellent soldiers. In this connection it is interesting that the Nazis and Gillespie of the Royal Air Force depend more on estimation of the character and temperament of the inductee than on any formal tests. In the light of the experiences of the last three years it is apparent that mobile warfare is not as liable to cause psychoneuroses as trench warfare was, probably because in mobile warfare there is more opportunity to express aggression adequately. The evacuation from Dunkirk produced a number of cases of acute neuroses, which disappeared completely under a few days of treatment.

Porter believes it is important to study groups of soldiers, selected on the basis of their family and past histories, because only from such a study can any real criteria for future selection be obtained. It is important, also, after an inductee has entered the service that a careful study of him be made in order to fit him into his proper niche.

PEARSON, Philadelphia.

ELECTRO-ENCEPHALOGRAPHIC STUDIES OF PSYCHOPATHIC PERSONALITIES. DENIS HILL and DONALD WATTERSON, *J. Neurol. & Psychiat.* 5:47 (Jan.-April) 1942.

Hill and Watterson made electroencephalographic studies on 151 patients with psychopathic personalities and compared the observations with those made on 52 control patients. The psychopathic patients were divided into aggressive, inadequate and mixed types. The last included persons with neuroses, psychoses and epilepsy superimposed on psychopathy. Of the 151 patients, 48 per cent had abnormal electroencephalograms, of which 13 per cent showed abnormalities in the record during rest, 15 per cent after hyperventilation and 20 per cent under both circumstances. Of the total control group, 15 per cent had abnormal electroencephalograms, a higher figure than that given by other workers. The authors found in the family and personal histories of the controls with abnormal electroencephalograms many instances of aggressiveness, impulsiveness and irritability. Of 66 predominantly aggressive psychopathic patients, 65 per cent had abnormal electroencephalograms, while of 38 predominantly inadequate psychopathic persons 32 per cent had abnormal records. The electroencephalograms of purely delinquent persons and of subjects with sexual perversions were for the most part normal. Only 1 of 11 epileptic patients with aggression in the mixed group had a normal electroencephalogram. Thus, four times as many aggressive psychopathic and twice as many inadequate psychopathic persons as controls had dysrhythmia. The abnormal resting record as a single factor plays a greater part in the dysrhythmia of the nonaggressive group, while abnormal response to hyperventilation is of equal frequency in the two groups. A closer relationship between past injury to the head and dysrhythmia was found to exist in the non-aggressive than in the aggressive group. Epilepsy, though a rare factor in the authors' material, when associated with aggressive psychopathy produced a higher percentage of abnormal electroencephalograms than when either condition existed alone. Aggressive bad temper was found nearly three times as frequently among the first degree relatives of aggressive psychopathic patients as among persons of the inadequate group, and dysrhythmia was more common in the former group with such a family history. The results prove that the electroencephalogram is consistently abnormal in aggressive psychopathic subjects. This may have its explanation in a failure of development or in immaturity of the central nervous system in such psychopathic persons, since similar abnormalities of the electroencephalogram are found in young children.

N. MALAMUD, Ann Arbor, Mich.

THE WAR AND NERVOUS DISTURBANCES. LEOPOLDO BARD, *Arch. brasil. de med.* 32:83 (March) 1942.

Bard notes briefly that disturbances of the nervous system without underlying organic injury occur in time of war. The disturbances are more frequent among noncombatants than among combatants, and are frequent even among persons in neutral countries not involved in the actual conflict. Such people follow anxiously bulletins, journals and radio programs and react with depression, anxiety, apathy, lassitude, insomnia, hyperemotivity and similar symptoms. They are excessively sensitive, impressionable and suggestible. The author feels there is consolation in the fact that the symptoms are not grave and can be relieved rather easily.

BAILEY, Chicago.

Diseases of the Brain

PYRAMIDAL SIGNS OF THE UPPER EXTREMITY. O. LANGE, Rev. Assoc. paulista de med. 8:351 (June) 1941.

This scholarly article won a well deserved prize. The difficulty in eliciting objective signs of defect of the pyramidal tract from the upper extremity is familiar to all neurologists. The author has made a painstaking review of those which have been described, illustrates each of them and presents an interpretation of them in physiologic terms. Two tables summarize the contents of the book.

Pathologic Reflexes Resulting from Lesions of the Pyramidal Tract

Name	Stimulus	Response
Palm-chin reflex (Marinesco-Radovici)	Stimulation of hypothenar region (ulnar, median)	Contraction of muscles of chin and elevation of corner of mouth
Thumb-adductor reflex ("Babinski of the hand") Marie-Foix	Superficial stroking of hypothenar region (ulnar)	Adduction and flexion of thumb; sometimes flexion of adjacent digits and extension of little finger
Variations: Foxe Oppenheim Schäffer Gordon	Pinching hypothenar region Rubbing external surface of forearm Pinching tendons of palm Squeezing muscles of forearm	Same response
Extension-adduction reflex (Dagnini)	Percussion of dorsum of hand (radial)	Slight adduction and extension of wrist
"Mendel-Bechterew of the hand"	Percussion of dorsal aspect of carpus and metacarpus (radial)	Flexion of fingers
"Rossolimo of the hand"	Percussion of palmar aspect of metacarpophalangeal joint	Flexion of fingers
Hoffmann-Trömner sign	Squeezing or snapping nail of middle finger (median)	Flexion of thumb, sometimes of forefinger
Gordon's sign	Compression of region of pisiform bone (ulnar)	Extension of flexed fingers
Chaddock's sign	Pressure on tendon of palmaris longus muscle	Flexion of wrist; extension of fingers

Synkinesis of Upper Extremity in Cases of Pyramidal Lesions

Name	Stimulus	Response
Wartenberg's sign	Active flexion of fingers about a stick	Flexion and opposition of thumb
Sign of Klippel and Weil	Passive extension of fingers (when there is some contracture in flexion)	Flexion and opposition of thumb
Souques' sign of interosseus muscles	Active elevation of extended arm	Extension and abduction of fingers
Strümpell's sign	Active flexion of elbow	Pronation and flexion of hand
Brachibrachial synkinesis	Extension of flexed elbow of normal side by examiner against patient's resistance	Flexion of elbow on paralyzed side
Sterling's sign	Active adduction of shoulder on normal side against resistance by examiner	Adduction of shoulder on paretic side

Special Senses

THE CATATONIC PUPIL. ALEXANDER LEVINE and PAUL SCHILDER, *J. Nerv. & Ment. Dis.* 96:1 (July) 1942.

The catatonic pupil as described by Westphal is usually in middilatation, with a response to light varying from prompt contraction to absolute rigidity and changing from moment to moment. The size and equality of the pupils also vary. This type of pupil is a not infrequent finding in various types of psychiatric patients.

Certain mechanical procedures may influence the state of the pupil. The Redlich phenomenon is the production of pupillary rigidity due to strong muscular exertion in epileptic patients. In normal persons, as well as in patients with preexisting pupillary anomalies, the use of active pressure causes dilatation and diminution of the light reflex. A similar effect can be produced by pressure on the iliac point. To study these phenomena, a series of patients were selected in whom the pupillary reactions were impaired by the local instillation of various eye drops. The Redlich phenomenon was present up to the point of complete abolition of the pupillary reflex with homatropine or physostigmine. With cocaine it continued to be apparent even with the maximum effect of the drug. No pupillary effects were observed with the local instillation of a 15 per cent solution of mechoyl chloride or of a 4 per cent solution of acetylcholine.

The pupillary reactions were studied in a group of patients receiving nitrogen inhalation therapy for schizophrenia. It was noted that coincident with the occurrence of restless movements of the extremities, progressive dilatation of the pupils with lessened reaction to light appeared. It thus seems that the treatment situation brought about the semblance of a catatonic pupil. In those patients who exhibited this reaction before treatment, the disturbance was more pronounced after treatment. The authors conclude that the anoxic pupil resembles the catatonic pupil slightly, that in patients who have had previous anoxic therapy the treatment situation may provoke pupillary changes similar to those observed in catatonic pupils, that the pretreatment situation may produce severe changes in patients with latent tendencies toward catatonic pupillary reactions and that the catatonic pupillary changes and the effects of anoxemia reinforce each other.

Five patients who received erythroidine prior to metrazol displayed pupillary variations in the pretreatment stage. This drug itself produces such changes, and it is felt that the effect is additive.

The authors believe that the pupillary changes described are due to paralysis or inhibition of the parasympathetic nervous system. The effect of active and passive pressure is to cause a concomitant contraction of the abdominal musculature, with increase of the intra-abdominal pressure. This stimulates the splanchnic nerves, with resultant inhibition of the parasympathetic fibers.

CHODOFF, Langley Field, Va.

A STUDY OF THE HEMIANOPIAS. L. ROSEN, *Confinia neurol.* 4:271, 1942.

Rosen has made an analysis of the frequency, etiology and localization of the disease process in 97 cases of hemianopia. Injuries to the vascular system, namely, hemorrhage, thrombosis and embolism, were among the most frequent causes of lesions situated central to the chiasm. Tumors constituted the next most frequent cause, and syphilis came third. On the other hand, tumors were far more numerous in cases of the heteronymous hemianopias localized at the optic chiasm. In the group with vascular conditions by far the larger proportion of the patients were affected after the age of 40. About half the patients with chiasmal lesions were between the ages of 40 and 60 years.

DEJONG, Ann Arbor, Mich.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

H. HOUSTON MERRITT, M.D., *Presiding*

Regular Meeting, Oct. 15, 1942

Chronic Hypertensive Encephalopathy: A Clinicopathologic Report. DR. LOUIS GOODMAN, Howard, R. I.

Chronic hypertensive encephalopathy is a distinct clinical and pathologic entity. It belongs to the form of essential hypertension in which cerebral symptoms and pathologic processes may take precedence, or predominate, over cardiorenal changes.

Six cases, with complete autopsy studies, are presented. Patients of both sexes were affected. The average span of life after the onset of symptoms was eleven and four-tenths years. One patient lived thirty-one years. The average systolic blood pressure was 223 mm. of mercury, and the average diastolic pressure was 123 mm. No correlation could be established between blood pressure levels and duration of life. The average ages at onset and death were 40 and 52.6 years respectively. The majority of patients did not become frankly psychotic until the late stage of their illness. Many, however, exhibited transient mental symptoms and neurologic signs throughout the course of the disease. The development of frank and persistent psychosis seemed to be a bad prognostic omen as far as life was concerned.

Analysis of the comparative degrees of vascular disease and associated parenchymal damage disclosed that in the majority of cases both vascular and parenchymatous lesions were more severe and extensive in the brain than in any of the other organs of the body. The cerebrovascular arterioles were especially affected by a variety of pathologic changes. These changes included: (1) advanced hyaline and fibrocellular arteriosclerosis; (2) arteriolar and capillary thrombosis, with occasional recanalization of the thrombus; (3) intramural and perivascular hemorrhage; (4) perivascular round cell infiltration; (5) extensive fatty degeneration with aneurysmal dilatation of arteriolar walls, and, occasionally, (6) patchy hyalinized necrosis of the vascular walls.

Cardiac hypertrophy was not commensurate with the duration and the severity of the hypertension. In this respect, chronic hypertensive encephalopathy differs from malignant hypertension and benign nephrosclerosis. This difference may be explained by the fact that the patient with the process under discussion experiences hypertensive episodes. The latter provoke cerebral manifestations, which bring the patient to the attention of the physician. In the intervals between attacks the blood pressure may not be greatly elevated. Consequently, the heart is not placed under constant hypertensive strain. This lability of blood pressure may also account for the unusual duration of life of many patients with this disease, who may have a history of hypertension for many years.

Whether the changes in the central nervous system precede those in the kidneys and whether they have any bearing on the pathogenesis of hypertension are questions which are raised, but not answered, by the pathologic observations in some cases. The evidence indicates that if the kidneys are not primarily involved, irreversible arteriolar changes may develop later there and in other organs which may lead to a persistent state of hypertension.

Examination of the endocrine organs, including the hypophysis, thyroid, adrenals and pancreas, failed to reveal any fundamental changes which could be linked causally with the hypertension.

It is suggested that bilateral renal denervation in the early phases of the disease, when the blood pressure is labile, might prevent or delay the persistent hypertensive phase. Such an operative procedure would prolong the usefulness of the patient to his family and to the community, and sometimes might spare him from ending his days in a mental disease hospital.

DISCUSSION

DR. ROBERT S. PALMER: Dr. Goodman's well studied cases illustrate a primary fact I have noted in following a large number of patients with hypertension, namely, that in 4 out of 5 the disease has a long course and that however severe it seems to be, most patients live to be at least 50 years of age. This is true of a little over 600 patients I have followed in the clinic and in private practice in the past ten years, not all of them for that length of time, but all for a considerable period. The exception lies in 10 per cent of patients who have severe

general arterial or arteriolar disease at a very early age. In his thirties such a patient behaves like a person in his sixties (with coronary disease, diabetes, cerebral vascular disease, etc.). Something like another 10 per cent of old patients with hypertension have a severe disease which is called "malignant hypertension," characterized by a rapidly advancing process with extensive arteriolar spasm. These two groups of patients die young. The rest live to be 50 or more and die with various manifestations of senile vascular change in the head, heart or kidneys. The senile changes, it is assumed, are hastened by intravascular pressure.

The cerebral manifestations of patients with hypertension at different ages seem to fall into categories similar to the manifestations of peripheral vascular disease in the extremities. In old age shrinking of the cortex and areas of softening (similar to arteriosclerotic disease of the extremities) are present. In the middle years there may be sclerosis and spasm (hypertensive crises and/or thromboses). In the forties and below a very different picture is apparent, one of vasospastic nature, similar to vascular disease in the extremities of young adults. My associates and I have had an opportunity of making extensive observations on a few such persons. For instance, a physician's wife, in her early forties, had a history of severe headaches which had been growing in frequency and severity for five or six weeks. Her blood pressure had been normal until a year and a half prior to the onset of headache. The hypertension was of moderate degree, but three or four weeks previous to her consulting me a syndrome of increased intracranial pressure developed, with slowing of the pulse, a disorder of the respiratory rhythm, papilledema, exudate and hemorrhages in the fundi. Lumbar puncture at first consistently revealed a greatly increased initial pressure. Reduction in the pressure relieved the symptoms temporarily. Finally, during a rapidly developing episode of apparent increase in intracranial pressure, the spinal fluid pressure not only was not increased but was even lower than normal. The pulse was slowed; the patient was semiconscious; the breathing was irregular. The diagnosis of a probable pressure cone was made, and cerebral decompression was done. The operator stated that there was an excess of fluid and bulging of the brain substance. In our minds there was no doubt that the decompression was a life-saving procedure, and one which gave place to definite clinical improvement. This operation was followed by lumbodorsal sympathectomy, carried out according to the technique of Smithwick, and the patient was discharged to return home with a blood pressure within normal limits, although the diastolic pressure remained slightly high. We have had 6 or 8 patients with similar conditions, some of whom had a decompression and subsequent sympathectomy which we think was life saving. Patients who had no operative treatment died. Autopsy revealed no recognizable lesion of the brain. We suspect that there may be a compensatory spasm of the cerebral vessels in younger patients with malignant hypertension, which results in cerebral ischemia and cerebral edema, with consequent increased intracranial pressure. Patients who do not have such a degree of increase in the intracranial pressure may have papilledema, which comes and goes under observation. The vessels of the fundi are always greatly constricted. Exudate and hemorrhages may or may not be present. In a few, about 40 per cent, of patients with, as we believe, true malignant hypertension, we seemingly obtained excellent results with sympathectomy performed before there was cardiac injury or real, irreversible damage to the kidneys. In these patients the papilledema entirely disappeared, as did the arteriolar spasm and the exudate and hemorrhages. Some of these patients we have observed for over three years since operation.

In my opinion, "hypertensive encephalopathy" refers to the disease in young adults with what appears to be spasm of the cerebral vessels, to the condition of young patients with extensive, precocious arteriolosclerosis and to the extensive arteriosclerosis of the older patients. One wonders what causes the cerebral ischemia and whether as a result of lowering of the general blood pressure by sympathectomy, there is relaxation of the retinal vessels, and possibly of the cerebral vessels. We believe that in patients with malignant hypertension papilledema and cerebral edema may result from a protective reflex vascular spasm in the retina and cortex, and that when sympathectomy is successful in lowering the general hypertension this vascular spasm is reduced. The physiologic, pulsatile blood flow returns, and the edema, exudate and minute hemorrhages are absorbed. This concept is highly theoretic at the moment, but it offers an explanation of the extraordinary improvement following reduction of the blood pressure in certain cases in which ordinarily one would expect the disease to advance rapidly to a fatal conclusion.

DR. H. HOUSTON MERRITT: This clinical picture has always been a puzzle to me. There must be massive cerebral edema.

DR. CHARLES S. KUBIK: There does not seem to be any agreement as to what constitutes hypertensive encephalopathy. The changes in most of Dr. Goodman's cases were those of arteriosclerosis and arteriolosclerosis. Such changes are likely to be noted when hypertension has existed for a number of years and are almost sure to be present when there have been cerebral symptoms. The small arteries and arterioles within the substance of the brain have

thickened, degenerated walls and small lumens, often occluded by concentric narrowing and thrombosis. There may be no large infarct, but numerous small foci of infarction and incomplete degeneration may be noted. The terminal event may be a large infarct or a massive hemorrhage.

It is easy to understand why there should have been cerebral symptoms in the cases described by Dr. Goodman, whatever the cause of the arterial and arteriolar disease may have been. But in the group of young adults with hypertension, mentioned by Dr. Palmer, the cause of the symptoms is not clear. Sometimes there is unconsciousness or stupor, without focal signs or increased intracranial pressure; it is thought that uremia can be ruled out. Patients in such a state may regain consciousness and live many months.

What is going on in a condition of this kind? The pathologist cannot say; so the clinician is told that it is vascular spasm, but many are not satisfied to make such an assumption on the basis of negative findings. It is possible that more thorough pathologic examination might reveal something, though I think that clinical studies are more likely to provide leads.

I was interested in Dr. Goodman's reference to aneurysm. I have never seen what I should be willing to call an aneurysm of an intracerebral artery.

DR. LOUIS GOODMAN, Howard, R. I.: I believe that hypertensive encephalopathy is a form of essential hypertension occurring in young or middle-aged persons characterized by cerebral, rather than by renal, symptoms and pathologic changes.

I share the feeling expressed by Dr. Merriitt that the term chronic hypertensive encephalopathy is unsatisfactory, but I do not know of any other which adequately describes a condition that differs both clinically and anatomically from other types of hypertension. I should like to emphasize again the relatively small hearts observed in patients with this disease despite a prolonged history of hypertension. In so-called benign nephrosclerosis, in which hypertension may be present for a number of years, pronounced cardiac hypertrophy is outstanding. The longevity in cases of chronic hypertensive encephalopathy distinguishes this condition from malignant nephrosclerosis.

I agree with Dr. Palmer as to the role of cerebral vasospasm in the production of cerebral lesions and symptoms. One encounters considerable histologic evidence to support the impression that vasospasm is associated with this disease. Almost always one may observe vessels with intramural hemorrhages, associated sometime with thromboses in the region overlying the hemorrhage. In a case of myocardial infarction microscopic preparations disclosed only partial occlusion of the lumen of one of the coronary arteries by a thrombus superimposed on an area of intramural hemorrhage. I believe that repeated attacks of cerebral vasospasm, with perivascular softenings and edema, establish the basis for the essential pathologic picture that develops later and account also for the prolonged clinical course of the disease.

In this connection, I should like to mention a man, aged 31, with hypertension, who is now under observation in the hospital with which I am associated. This patient had a severe cerebrovascular insult, which left him with right hemiplegia, aphasia and mental symptoms. All these manifestations characteristically receded spontaneously and fairly rapidly. Studies revealed that when he was under emotional stress his blood pressure showed a striking lability of both the systolic and the diastolic pressure. When he was at rest his blood pressure was only slightly elevated. This observation has been duplicated in similar cases. We believe that this lability is frequent in persons with this form of hypertension and that it may explain the slight cardiac hypertrophy and the patient's survival through many years of hypertension.

I have stressed arteriolosclerotic changes in this disease because they are more important than lesions in the larger arteries. One sees advanced cerebral arteriosclerosis in elderly patients without corresponding degrees of parenchymal damage. This is not true, however, of sclerotic changes in the arterioles of the brain.

Aneurysm may be demonstrated in benzidine and in sudan III preparations in cases in which severe fatty degeneration of the vascular wall predisposes to dilatation and hemorrhage.

Control of Clonic Responses of the Cerebral Cortex. DR. ARTURO ROSENBLUETH.

In rhesus monkeys, under anesthesia induced with chloralose (a compound of chloral hydrate and dextrose), electrical stimuli of appropriate intensity, frequency and duration elicit self-sustained responses in any region of the cerebral cortex. These responses may be recorded electrically. They exhibit several phases, with decreasing rates of cortical discharge. The last phase has a frequency similar to that of the muscular contractions in the clonic state of experimental epilepsy; it may, accordingly, be designated as "cortical clonus."

Rosenblueth, Bond and Cannon (*Am. J. Physiol.* **137**:681, 1942) observed that stimuli with an adequate slow frequency applied to an appropriate cortical area can control the rate of the self-sustained cortical clonus of that region. These stimuli can also prolong the response beyond its intrinsic duration. The expression "controlled cortical clonus" is used to designate the activity produced by these stimuli.

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Rosenblueth, Bond and Cannon (*Am. J. Physiol.* **137**:681, 1942) observed that stimuli with an adequate slow frequency applied to an appropriate cortical area can control the rate of the self-sustained cortical clonus of that region. These stimuli can also prolong the response beyond its intrinsic duration. The expression "controlled cortical clonus" is used to designate the activity produced by these stimuli.

The controlling relationships between different cortical areas may be summarized as follows: (a) There are pairs of areas with mutual, two way control; i. e., stimulation of either can control the clonic activity of the other. (b) There are pairs of areas which exhibit only one way control. (c) There are pairs of areas with no mutual controlling relationship. (d) It is possible to set up second, or higher, order controls, and thereby link areas which are not directly coupled; i. e., if area α controls area β and area β controls area γ , and area α does not control area γ directly, area α may control area γ via area β if both area β and area γ are activated simultaneously. (e) If electrical stimulation of one area controls the clonic activity of another, the self-sustained clonic discharge in the first will also control the discharges in the second. (f) It is possible to set up simultaneous, independent, self-sustained responses in areas of the type described in c.

From the results of sections of the gray matter, it is concluded that there are specific, long, subcortical functional pathways that link certain areas with several others. These pathways differ from those involved in the spread of self-sustained activity in the cortex.

The data lead to the following additional inferences. (a) The stimulation of a given area that initiates a self-sustained response builds up a prolonged state of enduring excitation in some cells of that area; this excitation evokes the clonic bursts during the response. (b) The excitation subsides gradually, as indicated by the progressively decreasing frequency of the spontaneous bursts. (c) The discharges cease when the excitation drops below a critical level. (d) There still remains, however, enough background excitation so that impulses from another area may trip further clonic bursts. (e) The end of the driven bursts indicates further wane of excitation below a second critical level. (f) Each clonic burst increases the background excitation both in the discharge area and in similar elements in other areas. (g) A self-sustained response which has spread to many areas will endure throughout as long as one of the active regions has enough background excitation for clonic activity and can control the others directly or indirectly, but the response will suddenly stop everywhere when excitation drops below the critical level in the last controlling area.

DISCUSSION

DR. WILLIAM G. LENNOR: This paper impresses me as an important contribution to an understanding of how the brain works. Dr. Rosenblueth has given his data, and I have no criticism of his conclusions. I wonder whether these observations might be applied to abnormal cerebral disturbances in man. For example, might one stimulate the brain in an appropriate place and neutralize the abnormal discharge which leads to a seizure? If the rate can be altered, perhaps the grand mal seizure could be changed to the petit mal type. Treatment of epilepsy with electric shock is being used in various clinics. Patients themselves have found that a sensory stimulus may inhibit a focal fit. A patient of Galen's teacher demonstrated that he could abort his jacksonian seizures by squeezing the part where the seizure began. Sensory stimulation must be in close proximity to the place from which the motor convulsion is originating. But in other types of seizures apparently other types of stimuli will act. Dr. and Mrs. Gibbs have often demonstrated that certain seizure discharges of the cortex can be modified by cerebral activity. These discharges must have a neurologic explanation, such as Dr. Rosenblueth gave in his animal experiments. Has Dr. Rosenblueth made any microscopic examination of stimulated tissues to see whether the nerve cells were damaged by the repeated stimuli?

DR. JOHN ADAMS ABBOTT: To a person who has been concerned only with clinical electroencephalography, one of the most interesting features of this paper is its scientifically satisfactory confirmation of something that one apparently sees in clinical electroencephalographic work but about which one can only conjecture, without scientific tests. I refer to the disturbances of cortical activity which are apparently caused by lesions remote from the part of the cortex at which the disturbance is observed.

Clinically one sees this most strikingly with unilateral lesions of the temporal lobe. In such a condition the stronger disturbance may occur on the side of the lesion, while a minor disturbance is apparent at a symmetrically opposite point on the other side of the head. It is supposed that the minor disturbance is a secondary focus due to nerve impulses from the primary focus at the site of the lesion. Dr. Rosenblueth's work seems to justify this supposition. Lemere published a clinical paper which is based on this theory, but in which the reported observations are almost too good to be convincing. It is a pleasure to the clinician when the physiologist produces such brilliant evidence of processes that for him must be largely a matter of conjecture.

DR. ARTURO ROSENBLUETH: Good tonic-clonic responses may be obtained from any part of the brain. I have had no experience with animals under ether anesthesia. McCulloch tells me the same thing is true for dial as for chloralose anesthesia. Monkeys are susceptible to anesthetics. The dose of chloralose a monkey requires is much smaller than that a cat or a dog requires. Perhaps this is the reason that it is difficult to get the right dose of ether.

I have not made any microscopic examinations, but I have worked for many hours on the same animal. The monkeys give the same responses at 11 o'clock at night that they do at 9 o'clock in the morning. I do not believe any damage is done to the cortex.

I did not comment on the fact that clonus can also be controlled by stimulation of the sciatic nerves. The stimulation will drive the clonic responses in several areas, i. e., areas 1, 4, 7 and 9 in each hemisphere, into the arm, leg and face divisions of corresponding areas; that does not appear to be the counterpart of the clinical observation. All I could do by means of electrical stimuli was to increase preexisting responses, never to diminish these responses.

H. HOUSTON MERRITT, M.D., *Presiding*

Regular Meeting, Nov. 19, 1942

Psychiatry in War. DR. EMILIO MIRA.

War can be considered as a period of existence in which groups and individuals must learn to live under new and difficult conditions, no matter who they are or where they are. This new mode of living breaks established habits, affections and beliefs and requires rapid adjustment to a new code of social duties and relations.

In time of peace, even under the more tyrannical regimes, a certain amount of privacy, initiative and freedom is permitted to the citizens. In time of war all that is not prohibited tends to become obligatory; thus there is a progressive absorption of the individual by the war machinery. Consequently, the individual loses all possibility of forecasting or planning his future and feels himself plunged into a dangerous, difficult, puzzling present.

During war psychiatry must take care to avoid as much as possible the evil results of such a tremendous change and must profit from its knowledge of the imperfections of the human mind in order to prevent failures in the application of human energies, especially of the thinking processes of those who carry the heavy responsibilities of planning and conducting the war strategy. Psychiatrists must not and cannot wait until mental trouble becomes apparent and evident, but must prevent it by a close and permanent collaboration with psychologists and selecting officers. This will lead not merely to getting "the right man in the right place," but—much more important—to getting "the right task in every place and at every moment for every man."

The recent Spanish civil war was rich in experience which showed that it is convenient for the trained psychiatrist to watch and control the overstrained chiefs and commanders, just as the medical expert on aerial medicine takes care of the state of his pilots, thus preventing errors and accidents. It is much more important to get a rest for an exhausted chief of the general staff than to select accurately a hundred soldiers. Military men are too proud of their duties to reveal that they are feeling overworked or exhausted. On the other hand, the removal of a military chief may have a bad effect on the morale and the organization of the sector under his command, unless it can be properly justified by a technical expert. Hence, objective tests are badly needed in order to detect, not the interests or the aptitude of any given man, but rather his mental fitness at a given moment, i. e., how he will use his mental power at that moment. I have been successful in creating certain tests, based directly on performance. Of them, I prefer the myokinetic psychodiagnosis test, which is able to detect the state of the basic attitudes of reaction of the subject within ten minutes. This test can easily be employed in the field and can be recommended to military psychiatrists working under emergency, as they almost always do. The technic and results of the myokinetic psychodiagnosis test will be fully described in the published volume of the Salmon Lectures of this year, but it can be outlined, in its simplest form, as consisting of a pencil test which permits the evaluation of the amount and direction of involuntary shiftings of the subject's hands when trying to perform small oscillatory movements in the fundamental directions of space. In right-handed subjects the right side of the body is more expressive of the actual state of the cerebral activities than the left side, which is, in its turn, more expressive of the constitutional trends. This is reversed, of course, in left-handed subjects. Hence, the comparison between the results obtained on the two sides is illuminating in detecting the relative amounts of genotypical and paratypical leads which determine a given mental abnormality. Careful observations made on previously selected groups of professional people of psychotic and psychopathic personalities and of delinquents have confirmed the practical value of this new technic, which is now being standardized.

With respect to the organization of psychiatric services on the battle front, my experience is in favor of the creation of psychiatric clinics in the rear zone of each army (in the ratio of one bed per thousand soldiers served) plus a small number of mobile psychiatric emergency centers, so-called prefrontal centers because they are to be located no more than 15 or 20 miles (24 or 32 kilometers) behind the firing line. These centers are dependent on the corresponding psychiatric clinics but are attached to the campaign hospital, at the clearing center of the evacuating lines of each military sector. These emergency centers get not only the psychiatric casualties of the advanced zone, but those of the intermediate zone (i. e., the zone between them and the psychiatric clinic); this gives many subjects the surprise of being removed ahead, instead of being evacuated backward, when complaining of psychiatric disturbances.

CHICAGO NEUROLOGICAL SOCIETY

ARTHUR WEIL, M.D., *President, in the Chair*

Regular Meeting, Nov. 19, 1942

Psychoneuroses of War. DR. LEWIS J. POLLOCK.

The severe environmental changes to which man is subjected in war, namely, fatigue, loss of sleep, hunger, thirst, fear and other emotions and concussion, were not in themselves associated with the development of psychoneurosis during the time in which these changes occurred. In some instances, after the disappearance of one or more of them, a psychoneurosis developed. The symptoms of the psychoneuroses, except for the form following concussion, were similar irrespective of where the disturbance developed or what the preceding environmental change had been. Preoccupation with psychologic mechanisms has led to neglect of careful study and recording of physical changes. To understand fully the pathogenesis of the psychoneuroses of battle as compared with that of other types, it will be necessary to study more carefully the physiologic responses of man to the various severe environmental changes.

DISCUSSION

DR. LLOYD A. ZIEGLER: Conditions of war include the quick changes of pressure in blast, the heat of the desert or jungle, the cold of high altitudes and long and arduous work under difficult conditions, to say nothing of the enemy. Stresses of the battlefield are great, and, if they become great enough, nearly every one will break down sooner or later. Persons are conditioned differently with respect to stresses; what will break one will not break another. Predisposition is a definite factor, as Gillespie pointed out from his experience with the bombings in England.

The chief psychoneuroses are hysteria or substitution disorders that are based on mimicry, such as chameleons and butterflies display. Hysteria is really a misnomer, as is neurasthenia. Invalidism, or the irritable weakness syndrome, centers around an energy defect in a person goaded by ambition. Psychasthenia is also a misnomer. Compulsive-obsessive neurosis is a better name for the disorder, which is a repetitive and uncontrolled series of automatic acts to relieve obsessive feelings. The anxiety psychoneurosis is one of pathologic self defensiveness, and is the form most likely to appear on the battlefield. The patient has a rapid pulse, perspires and is inclined to get panicky. The disorder is often mistaken for toxic goiter. Hypochondriacal disorder is a misnomer, too. It implies a location under the cartilages, but the distress does appear elsewhere. Persons with such a disorder are nearly psychotic; they believe unusual things about their distresses and show other disintegrative features. Post-traumatic, or postconcussion, neurosis is apparently a misnomer, too, but this state—perhaps chiefly an affective disorder—may occur on the battlefield in the predisposed.

Whether a patient is psychoneurotic or psychotic is merely an academic question. Psychoneurotic persons may become psychotic and may have as well any disease that others have. The internist and the surgeon arrive at a diagnosis of psychoneurosis often through the absence of physical disease. The psychiatrist has a definite syndrome in mind, which represents a disorder of human nature already briefly sketched.

Dr. Pollock has, wisely in these times, stressed the types of psychoneurosis most likely to appear in battle.

DR. LEWIS J. POLLOCK: I am much interested in the correlation of stresses and effect; I do not think one can evaluate the degree of stress by what one observes. It is striking,

for example, to note the disappearance in England of even the expected cases of neurosis among the civilian population because of the responsibilities imposed by bombing. I think most here heard Dr. Gillespie discuss this phase.

Etiologic Factors in the Adjustment of Men in the Armed Forces. MAJOR D. LOUIS STEINBERG, Medical Corps, Army of the United States, and DR. MARY PHYLLIS WITTMAN, Elgin, Ill.

The paper presents the results of a differential study of the sociologic, developmental, personality and adjustment characteristics of (1) 158 men attached to the medical corps unit at Chanute Field, Rantoul, Ill.; (2) 22 patients in the psychiatric unit at Chanute Field, and (3) 87 patients in the veterans' unit at Elgin State Hospital, discharged from the army within the past eighteen months as mentally ill.

The results of the study apparently corroborate points previously described in the literature. Certain facts are established.

1. The results reported are those of a controlled experimental project. Thus, the prognostic significance of certain factors with respect to selectee adjustment in the armed forces is substantiated.

2. Certain standardized and objective psychologic technics for investigation of various personality factors are of both diagnostic and prognostic significance in evaluation of the etiologic factors associated with a prospective soldier's adjustment to military life.

Thus study, and the analysis of results, suggest certain points pertinent to present selection at induction and classification centers, as well as to possibilities for future research.

Psychologic technics (in addition to measures of intelligence) would be of value as part of the psychologist's armamentarium at induction centers in weeding out selectees in need of intensive psychiatric study, in order to determine their fitness for army service. Persons representing extremes of behavior maladjustment would be screened out.

We suggest the need of a rating scale by which the patient may be referred to the neuropsychiatric unit. Knowledge of the patient's reaction to the camp situation, to his fellow soldiers and officers and to the discipline of camp life and enforced contact with many other men would be an invaluable aid to psychiatric study prior to the patient's induction into the hospital. Some idea of how and with whom the patient spent his leisure time in camp and how he was treated by his fellows, together with a description of the onset of his difficulties and the behavior that led to his referral to the neuropsychiatric unit, is important for the proper understanding, treatment and ultimate disposal of the patient. In addition to valuable insight into the dynamic mechanisms in the individual case, which it is at present difficult or impossible to obtain, this rating scale could be used in follow-up studies, as outlined in the paper.

DISCUSSION

DR. PHYLLIS WITTMAN, Elgin, Ill.: We regret that for the purpose of oral presentation we had to omit from our paper the orientation (discussion of previous studies in this field), as well as the detailed analysis of our results. We considered our observations particularly significant because the study was controlled; that is, we are able to say definitely that certain traits and developmental characteristics are associated with the selectee who is unable to make a satisfactory adjustment at camp, for these traits significantly differentiate the maladjusted from the well adjusted control group.

We hope to continue our project by studying a group of guardhouse prisoners, to find whether the psychopathic personality, as well as the psychoneurotic selectee, can be differentiated from the well adjusting controls.

DR. W. S. McCULLOCH: Conditions in barracks are like peace conditions. Fighting is another story. My recollection of the last war may be illustrated by 2 instances. A man who came back from France with probably the greatest number of medals suffered from the most severe form of hysteria that I have ever seen. Again, an officer who was beloved in the Navy, and was known as "the old lady" was about as neurotic a person as one could find, but he has subsequently distinguished himself. I have often wondered whether in segregating persons with neuroses one may not be eliminating many men who might be good material under conditions of hazard.

MAJOR D. LOUIS STEINBERG: Of course there are certain persons who succeed in spite of the apparent predominance of personality characteristics that, on the surface, augur for poor adjustment, but it is possible that closer studies of these persons would show other characteristics which counterbalance their undesirable traits and explain their apparent success. Our point is that certain persons are not able to adjust in camp life; it would be of

benefit both to the government and to society if a method could be devised for detecting and sifting out these men before they are inducted into service. Even though occasionally one might remove one or two men who might have made good, I believe the error would still be in the other direction and that all those unfit for military service would still not be discovered immediately; however, by the use of such inventory scales as we have presented, a major number of misfits would, I think, be caught prior to their induction into the service.

An Unusual Complication of the Intraspinal Use of Iodized Poppyseed Oil. DR. PAUL C. BUCY and DR. IRVING J. SPEIGEL.

A man aged 36 suffered from spondylolisthesis, for which fusion of the lumbosacral portion of the spine had been effected in April 1937. In March 1938, because of the development of sciatica on the left side, iodized poppyseed oil was injected intraspinally. Fluoroscopic examination revealed that some of the oil had lodged at the level of the eighth thoracic vertebra and had remained there. Late in 1941 there developed progressive symptoms of involvement of the spinal cord at that level. Lumbar puncture in February 1942 showed almost complete spinal block. At operation, on March 10, 1942, two collections of encysted iodized poppyseed oil in the subarachnoid space and a greatly thickened arachnoid membrane were observed and removed. Within a few weeks the patient made a nearly complete recovery.

From a study of the case the following conclusions were reached: 1. The patient suffered from localized adhesive arachnoiditis at the level of the eighth thoracic vertebra prior to injection of the iodized poppyseed oil. 2. This arachnoiditis caught and held some of the oil, which, in turn, stimulated fibroblastic proliferation in the leptomeninges, thus increasing the arachnoiditis and resulting in dysfunction of the spinal cord. 3. Although the intraspinal injection of iodized poppyseed oil is ordinarily an innocuous procedure, the existence of a lesion which retains the oil in contact with the spinal cord may ultimately result in undesirable changes in the cord.

DISCUSSION

DR. A. EARL WALKER: This paper raises the interesting question of the late complications of intrathecal injection of iodized poppyseed oil. It is true that serious results have been reported, but these effects have occurred within a few days of injection. It has been stressed that the reaction is more severe in the presence of arachnoiditis. In the ordinary case iodized poppyseed oil gives rise to little reaction. In the present case one wonders what role the previous lesion played in the appearance of symptoms from two to two and a half years after the injection of the iodized poppyseed oil. That seems rather a long time for arachnoiditis, if due to the presence of the iodized oil, to make its appearance. The ordinary reaction to iodized poppyseed oil usually occurs within a few months.

DR. PERCIVAL BAILEY: I am not convinced that the iodized poppyseed oil had anything essential to do with the symptoms. Certainly, the rapidity of recovery after operation could not be considered as evidence. I have seen just as rapid subsidence of symptoms when iodized oil had not been injected. The arachnoiditis recurred within a few months, and I should be interested in knowing whether it recurred in this case.

DR. IRVING J. SPEIGEL: At present the patient is almost completely recovered. We appreciate the possibility of a recurrence of his previous symptoms, and with that in view we are watching his progress carefully.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

JOHN M. DORSEY, M.D., *President, in the Chair*

Regular Meeting, Nov. 12, 1942

Bilateral Ageusia Associated with Unilateral Bell's Palsy. DR. GERALD O. GRAIN, Detroit.

For several years, in examining patients with facial palsy of peripheral type, I have observed that the sense of taste was impaired not only on the affected side, but on the supposedly good side. This observation has been made so frequently that it has become to me a matter for surprise to find normal gustatory sense on the contralateral side in any case in which ageusia accompanies paralysis of the face.

Exclusive of cases of facial paralysis of obvious intracranial and extracranial origin, 157 cases could be presumed to be instances of facial neuritis, or Bell's palsy. In only 77 of this number was there a record of examination of the sense of taste, and in only 40 cases was there indication that the sense of taste had been adequately tested for both sides of the tongue. In 36 of the 40 cases taste was impaired and in 4 it was not impaired. In 6 of the 36 cases there was unilateral impairment of taste on the same side as the palsy and in 30 of the cases impairment of taste was bilateral. The degree of ageusia, either homolateral or contralateral, showed no relation to age. The contralateral ageusia was of less intensity than the homolateral ageusia in 25 cases, of equal intensity in 5 cases and of greater intensity in no case. The contralateral ageusia was of lesser intensity than the palsy in 23 cases, of equal intensity in 4 cases and of greater intensity in 3 cases. In no case was unilateral ageusia present on the side opposite the palsy. The degree of contralateral ageusia was graded as slight in 11 cases, moderate in 9 cases, pronounced in 8 cases and severe in 2 cases. In 1 case there was evidence of initial transitory palsy on the opposite side.

To explain this observation on an anatomic basis, a dissection was made of the tongue in an attempt to detect the presence of overlapping terminal fibers from the two sides. Such overlapping could not be demonstrated grossly. In a clinical case in which one lingual nerve had been rendered anesthetic by nerve block for tooth extraction, both anesthesia and ageusia were found to end sharply in the midline of the anterior two thirds of the tongue. The existence of a variety of alternative pathways for the afferent fibers for taste suggested in the past is now believed to be a misconception, and all taste fibers from the anterior two thirds of the tongue are now assigned to the chorda tympani and the nervus intermedius of the seventh cranial nerve. In the brain stem there appears to be no other secondary gustatory tract than that crossing wholly to the opposite side from the nucleus of the fasciculus solitarius and ascending to the thalamus, and thence to the cortex at the base of the posterior central gyrus. Thus, no explanation for bilateral gustatory impairment on the basis of an exchange of afferent pathways between the two sides can be derived from anatomic considerations. This forces one to the conclusion that cases of this condition represent bilateral facial neuritis, manifested on the side of lesser involvement by a gustatory lesion only.

Prognostic Possibilities of the Rorschach Method in Metrazol Therapy. MR. WOODROW W. MORRIS, Pontiac, Mich.

The present study is an attempt to determine whether the Rorschach method reveals any signs or patterns which are predictive of success in treatment with metrazol of a more or less general cross section of psychotic conditions. After the completion of treatment, the patient's clinical course in the hospital or at home was carefully followed. The final judgment as to the success or failure of the treatment was based on the patient's overt condition, rather than on the opinion of the staff physicians, as it was felt that such a basis of judgment was more reliable. Forty-one patients were included in this study—15 men, with a median age of 28 years, and 26 women, with a median age of 37 years. The duration of illness ranged from less than six months to more than twelve years, with a median duration of three and nine-tenths years. Of the total number of patients, 44 per cent were improved, and 56 per cent were unimproved. The highest rate of improvement was noted in the manic-depressive patients.

Cursory examination of the data received from the several Rorschach factors for the patients of the two groups, namely, those who improved and those who did not improve, eliminated a number as prognostically insignificant; others proved to be significant in varying degrees. In general it was found that the patients who benefit from treatment are those who are more intact and who are living on a higher intellectual, social and cultural plane than those who do not improve. Each of the more significant factors was then studied further in an effort to determine a critical figure for each that might more specifically differentiate the two groups of patients. These signs were weighted in the order of their significance in differentiating the groups, as follows: Less than 15 per cent of "anatomic" responses and less than 17 per cent of "O" responses were weighted as 3 points each, since they were statistically most significant. Less than 2 per cent of "color form" responses and more than 1 per cent of "space" responses were weighted as 2 points each, while more than 13 per cent of "normal detail" responses and more than 70 per cent of "good perception" responses received a weighting of 1 point each. It was found by the chi-square test that the application of these six signs weighted as described differentiated the two groups to a significant degree and that a total of weighted points equal to or greater than 7 suggested a good prognosis. Selection of patients for therapy on purely clinical grounds yielded an improvement rate of 44 per cent, with a concomitant loss of 56 per cent. By application of

the six prognostic signs, the improvement rate was raised to 64 per cent, an increment of 20 per cent over that obtained by clinical selection.

Diagnosis and Surgical Pathology of Certain Types of Sciatic Neuritis. DR. ALBERT S. CRAWFORD, Detroit.

Neurosurgeons have in the last few years brought about a new surgical approach to the problem of relief of pain in certain of the noninflammatory types of sciatic neuritis. At first the chief interest was focused on the intervertebral disk, and later, on the ligamentum flavum. A number of large series of cases have been reported from prominent medical centers which establish lesions of these structures as real surgical entities. In such cases a history of trauma is common, and persistent or recurring sciatic pain, with absence of the ankle jerk, is constant. At first iodized poppyseed oil was used as a diagnostic and localizing means. Later injection of air became more popular, and more lately pantopaque is promising to become an even better means of localization because, while it is as opaque as iodized poppyseed oil, it is more easily removable, if necessary. (Pantopaque is a new radiopaque oil that is thinner and less viscous than the older iodized oils. It has been developed at the University of Rochester and is still in the experimental stage and not yet on the market.)

The surgical approach has been by simple laminectomy. At first the procedure was more radical. Gradually it was found that localized rupture of the intervertebral disk could be exposed and the disk satisfactorily removed by means of a hemilaminectomy, and in some cases with practically no removal of bone. The end results have proved to be excellent.

My experience has been in accord with that of others, but I have found that there is another group of patients with chronic recurrent involvement of the sciatic nerve in which the pain is due not to ruptured intervertebral disk but to pressure on the nerve in the intervertebral foramen by a combination of one, two or more of the adjacent structures in the foramen, such as the ligamentum flavum, an overhanging facet, a prominent or thickened, but not ruptured, intervertebral disk or chronically thickened tissue, including enlarged veins, accompanying the nerve in the foramen. To these cases can be added some in which the pain is due to pressure on the nerve from the lesions of hypertrophic arthritis or adhesions to nerves resulting from former injections of alcohol or previous inflammatory processes.

In this entire group, 70 per cent of over 80 cases, the history of trauma was less definite, but the pain was chronic, recurrent and resistant to conservative orthopedic management and was sufficient to incapacitate the patient. The clinical and localizing signs and symptoms were often as definite as those with ruptured intervertebral disk. They were at times bilateral and involved most frequently the fourth or fifth lumbar nerve.

In many of these cases the more limited exposure did not reveal the entire cause, and only when the nerve was followed outward through the foramen was the cause of the trouble apparent. Sometimes this dissection necessitated partial removal of one or two facets, at times with a chisel. In most cases the trouble seemed to be a combination of one, two or even three of the aforementioned factors. If the lesion was known to be bilateral, an excellent exposure was obtained in some cases (10 in all) by removal of bone with a chisel and by sharp dissection of one entire dorsal arch, with the attached facets. After the nerves were adequately decompressed, the removed dorsal arch was fastened in its proper place with stainless steel wire. In such cases the patient has done well afterward, convalescence has been shorter than when bone grafts were done, and complaints of weak back have not been encountered.

From this experience I have concluded that there is an increasingly large group of cases of chronic, intractable, incapacitating sciatic pain in which operation should be carried out. The cause of the pain may not be a ruptured intervertebral disk, but if the exploration is extensive enough, the compressing or impinging tissue will be seen. If this has been adequately removed, there has been relief of pain in 90 to 95 per cent of cases. I offer a method of limited bilateral decompression, with replacement of the dorsal arch to eliminate the possibility of a subsequent weak back.

JOHN M. DORSEY, M.D., *President, in the Chair*

Regular Meeting, Jan. 14, 1943

Psychiatric Study of a Man with a Convulsive Disorder. DR. LEO H. BARTEMEIER, Detroit.

A psychiatric study was made of a patient who presented the characteristic manifestations of idiopathic epilepsy. Various examinations for organic disease of the central nervous system revealed nothing significant. An understanding of the preconvulsive period and its relationship

to the later convulsive disorder is important. The study revealed that the whole early mental development of the patient had been influenced by the mother's overprotective attitude, which had seriously interfered with the natural development of the patient's aggressiveness. The aggressiveness was later forced into a pathologic mode of discharge represented by the attacks. The convulsive disorder was precipitated by two traumatic surgical experiences. The relation between the patient's anxiety and his seizures was demonstrated by several episodes which occurred during the course of the treatment. Although the patient had to continue medication with phenobarbital, his improvement was greatly enhanced by the psychotherapy.

DISCUSSION

DR. HARRY E. AUGUST, Detroit: Among the forms of epilepsy usually classified as idiopathic is a condition which may be termed psychic epilepsy. Many types of emotional disturbance may express themselves through the symptoms of epilepsy. One type frequently encountered under such circumstances is that of sadomasochism, in which the seizure represents a massive discharge of sadistic energy which is turned back on the patient. Dr. Bartemeier's case appears to fall into this classification, and a number of details have been dealt with speculatively from this point of view.

DR. RICHARD STERNA, Detroit: An important point expressed in Dr. Bartemeier's paper is that of etiologic combination, or the collaboration of hereditary and accidental factors. Dr. Bartemeier recently published a paper (*Bull. Menninger Clin.* 6:190 [Nov.] 1942) in which he presented Freud's contribution to mental heredity. Hereditary and accidental factors supplement each other in producing the final etiologic effect. Freud created the concept of complementary series in order to reach a better understanding into psychopathologic etiology. If the hereditary factors are slight, strong and impressive postnatal experiences are necessary to produce the psychopathologic result, and vice versa, strong heredity will require only slight outside factors to produce the pathologic manifestations. The validity of the concept is proved by the therapy. If the influence of the accidental factors is removed by psychotherapy, the hereditary factors recede, as it were, into latency.

In his present paper Dr. Bartemeier made a practical application of what he made theoretically so clear in his former paper. It is of extreme practical importance to investigate the possibility of accidental factors in the causation of epilepsy and to try to undo them, so that inner conflicts and tension are dissolved. If it is proved by more cases like Dr. Bartemeier's that the removal of accidental psychogenic factors in cases of epilepsy leads to relief and notable improvement, perhaps even to complete cessation of the seizures, the discovery not only would be of theoretic interest in the sense that the complementary series of outside and hereditary etiologic factors is valid in the case of epilepsy, but would be of tremendous practical benefit to persons stricken by this terrible disease.

Frequency of Convulsive Disorders in the Feeble-minded: Clinical and Patho-anatomic Considerations. DR. R. W. WAGGONER, Ann Arbor, Mich., and DR. J. G. SHEPS, New York.

Convulsive disorders in the feeble-minded present the most important problem in the care of such patients. In 10 per cent it is the cause of death. This paper is a report on the incidence of convulsive disorders in feeble-minded patients and the relationship between the convulsions and mental retardation. A series of 254 patients were studied pathoanatomically. Of these, 105 or 41.3 per cent, had convulsions. These all showed either residuals of an encephalitic process or malformations of the brain. There was no apparent correlation between the incidence of convulsions and either the degree of feeble-mindedness or the type of pathologic change in the brain.

DISCUSSION

DR. CARL D. CAMP, Ann Arbor, Mich.: From a statistical viewpoint it is important to know the source of the material studied. Institutionalized epileptic patients show a high proportion of feeble-mindedness, but for private patients the figures would be quite different. Contrary to public opinion, it is clear that epilepsy is not necessarily associated with feeble-mindedness.

DR. R. A. MORTER, Kalamazoo, Mich.: I have always been interested in the architecture of the brain of the feeble-minded. I have often wondered how the structure of the brain of the feeble-minded person differs from that of the normally intelligent person, and whether the abnormal structural deviation of the brain of the feeble-minded becomes greater with the lower levels of intelligence.

Book Reviews

The Rorschach Technique: A Manual for a Projective Method of Personality Diagnosis. By B. Klopfer and D. Kelley. Price, \$3.60. Pp. 405, with index. Yonkers, N. Y.: The World Book Company, 1942.

The Rorschach method of personality analysis is still a mystery to most neurologists and psychiatrists. It cannot be said that the present volume makes the matter simple, but the book does provide a great store of information about the test, which is far easier of access than that in Rorschach's original book or any others at present available. This history of the test is interestingly described; then precise directions are given for administering it. The method of scoring now recognized by the Rorschach Exchange is presented. Finally, the practical use of the test in clinical psychiatry and neurology is described. There is an exhaustive bibliography.

The test is useful in the differential diagnosis of various psychoses and neuroses. In addition, definite patterns of response are seen with certain types of structural disease of the brain. The specificity of the pattern in epilepsy is open to question.

It would be difficult, but not impossible, to learn to give and to interpret the Rorschach test from this book alone. The manual will, however, be of great value to all those who are working with the procedure, or who are attempting to utilize its results.

Roentgen Treatment of Diseases of the Nervous System. By C. Dyke and L. Davidoff. Price \$3.25. Pp. 198, with illustrations. Philadelphia: Lea and Febiger, 1942.

Additions to the means of treatment of disorders of the nervous system are always welcome. Roentgen ray therapy has been successfully applied to a surprising variety of neurologic diseases—chiefly to tumors, of course, but also to syringomyelia, herpes zoster and other conditions. The present book is a concise, scholarly review of the entire literature, with adequate historical material. Conclusions are drawn chiefly from the authors' own material, however. This has been extensive, well studied and critically reviewed.

The authors warmly recommend a prolonged trial of roentgen ray treatment in cases of chromophobe adenoma of the pituitary before operation is considered, except when vision is seriously threatened. They report good success, also, in cases of astrocytoma, oligodendroglioma and glioblastoma, conditions which are not usually regarded as favorable for treatment. They are somewhat skeptical of the value of the therapy for syringomyelia. The technic of treatment is carefully described.

This book belongs in the library of every neurologist.

Dark Legend: A Study in Murder. By Frederic Wertham, M. D. Price, \$2.75. Pp. 270, with 1 illustration. New York: Duell, Storm and Pearce, 1941.

This volume constitutes a serious attempt to study the psychologic implications in the murder of his mother by a boy of 17. It is a serious document, with good description and clear phrasing. It should serve as a contribution to the literature of criminal psychology and should be read by all interested in this field. As a study of the type of character which murders it is worthy of its author, and it can be highly recommended both as literature and as psychology.

Psychology You Can Use. By William H. Roberts. Price \$2. Pp. 246. New York: Harcourt Brace and Company, 1943.

This book should prove both entertaining and instructive to any one who has not had an introductory course in psychology and wants to know with what the science deals. It is a small volume which explains psychology in simple and readable form. The opening chapters are concerned with the physiologic approach to the understanding of human behavior and cover such topics as taste, smell, hearing and seeing. After this, the more truly psychologic fields are reviewed, and attention, learning, instincts, intelligence, emotions and other topics come up for review. In addition to the general exposition, each chapter carries suggestions for simple home experiments which the reader can try out by himself.

In his selection of material Professor Roberts has unerringly picked the essentials, and his presentation should prove satisfactory to all psychologists regardless of their orientation. There is one erroneous diagram used in the discussion of the Müller-Lyer illusion; aside from this the book is factually correct.

An additional merit of this book is the fact that, while the reader learns considerable from his study of this work, it does not pretend to give him anything which might make him feel he knew enough to give psychologic advice to others. The book is recommended for basic undergraduate orientation in the field.

INDEX TO VOLUME 49

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

- Abdomen:** See Gastrointestinal Tract; etc.
- Abnormalities and Deformities:** See under names of organs and regions, as Brain; etc.
- Abscess:** See under names of organs and regions, as Brain, abscess; etc.
- Acetylcholine:** See Choline and Choline Derivatives
- Acid, Ascorbic:** See Ascorbic Acid
- Barbituric:** See under Barbitol and Barbitol Compounds
- Cervitamic:** See Ascorbic Acid
- Lactic Acid:** See Blood, lactic acid
- Nicotinic:** See Nicotinic Acid
- Acid-Base Equilibrium** effect of alkalosis and acidosis on cortical electrical activity and blood flow, 286
- Acidosis:** See Acid-Base Equilibrium
- Activity, primacy of area 13 of orbital surface of cerebral cortex in production of hyperactivity in monkeys,** 780
- Adams, R. D.:** Occlusion of anterior inferior cerebellar artery, *765
- Addison's Disease,** electroencephalogram in, 137
- Adolescence,** prognostic factors of adolescent psychoses, 292
- reactions of people to war, 140
- Adrenal Preparations,** results of insulin and epinephrine tolerance tests in schizophrenic patients and in normal subjects, *195
- use of adrenal cortex extract in cases of insulin shock complicated by pulmonary edema: review of literature and report of case, 304
- Adrenals,** interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
- Age,** histochemical changes associated with aging; skeletal and cardiac muscle in rat, 912
- Old:** See Old Age
- studies in diseases of muscle; heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course, *641
- Ageusia:** See Taste
- Agraphia:** See Aphasia
- Akelaits, A. J.:** Studies on corpus callosum; relationship of grasp reflex to section of corpus callosum, *820
- Alcohol,** effect in experimental liver cirrhosis, 467
- Alcoholism:** See also Liver, cirrhosis and mental disorder, 608
- and mental disorder in Massachusetts, 1917-1933, 131
- conditioned reflex therapy of alcoholic addiction; follow-up report of 1,042 cases, 138
- predisposing factors in bromide intoxication, *359
- vitamin deficiencies and liver cirrhosis in, 135
- Alexander, L.:** Experimental studies on electric shock treatment; intracerebral vascular reaction as indicator of path of current, 617
- Alkalosis:** See Acid-Base Equilibrium
- Almy, T. P.:** Studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *12
- Altitude,** neuropsychiatric aspects of aviation medicine, 147
- Alzheimer's Disease:** See Insanity, presenile
- Amentia:** See Feeble-mindedness; Insanity; Mental Diseases; etc.
- Amnesia,** early symptoms of aphasia with brain tumors, 609
- Amyot, R.:** Meningeal gliomatosis secondary to intramedullary glioma, *383
- Amyotrophy:** See Sclerosis, amyotrophic lateral
- Anaphylaxis and Allergy:** See Asthma; Hay Fever; etc.
- Androgens,** testosterone therapy of involutional psychosis, 306
- Aneurysm, anillary;** relation of anomalies of circle of Willis to formation of aneurysms, 615
- Angioma,** calcification of cerebral cortex associated with meningotheiomas; meningioma; pathologic study, with comment on incomplete type of neurocutaneous syndrome, *507
- Angyal, A.:** Predisposing factors in bromide intoxication, *359
- Anomalies:** See under names of organs and regions, as Brain; etc.
- Anorexia:** See Appetite
- Anxiety:** See Neuroses and Psychoneuroses
- Aphasia** after major temporal lobectomy, 465
- Amnesic:** See Amnesia
- Apparatus:** See also Instruments
- electrical skin resistance technic used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454
- grouping behavior of normal persons and of persons with lesions of brain; further analysis, *489
- to be used in recording tremors, *123
- Appetite,** cachexia of mental origin; nature and management, 300
- Arachnoid,** circumscribed arachnoid sarcoma of cerebellum, 289
- Hemorrhage:** See Meninges, hemorrhage
- inflammation; foreign body granulomas produced by surgical cotton, *581
- inflammation; symptomatology and pathology of spinal arachnoiditis, 133
- inflammation; unusual complication of intraspinal use of iodized poppyseed oil, 926
- Tumors:** See under Meninges
- Arachnoiditis:** See Arachnoid, inflammation
- Arlett, S.:** Vascularization of cerebral neoplasms studied with fuchsin staining method of Eros, 626
- Arms:** See also Extremities
- pyramidal signs of upper extremity, 917
- Arnold-Chiari Deformity:** See Brain, abnormalities
- Arsenic and Arsenic Compounds:** See also Arspenamines
- encephalopathy following intravenous administration of arsenical preparations, *863
- Therapy:** See Syphilis
- Arspenamines,** cerebral lesions following administration of neoarsphenamine, 603
- Arteries:** See also Aneurysm; Arteriosclerosis; Blood pressure; Embolism; Pulse; Thrombosis; etc.
- Cerebral:** See Brain, blood supply
- occlusion of anterior inferior cerebellar artery, *765

- Arteriosclerosis, cerebral, histogenesis of, 622
 predisposing factors in bromide intoxication, *359
 psychopathologic review of senile and arteriosclerotic disorders, 299
- Artificial Fever Therapy: See Neurosyphilis
- Ascorbic Acid, presence and localization of vitamin C in central nervous system, 283
 studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
- Asthma, bronchial, incidence of neurosis in cases of, 914
- Ataxia, combination of Friedreich's ataxia and Charcot-Marie-Tooth atrophy in each of 2 brothers, 295
 hercdo degenerative cerebellar disorders, 610
- Atherosclerosis: See Arteriosclerosis
- Atlas and Axis, cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
- Atrophy: See also under names of organs and regions, as Bones, atrophy; etc.
 muscular: See also Dystrophy, muscular
 muscular; amyotrophic lateral sclerosis and related conditions; clinical analysis, *151
 muscular; combination of Friedreich's ataxia and Charcot-Marie-Tooth atrophy in each of 2 brothers, 295
 muscular; effect of electrical stimulation on atrophy of denervated skeletal muscle, *802
 muscular; some new applications of synthetic vitamin E therapy, 472
 muscular; studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
 muscular; treatment of certain muscular atrophies with vitamin E with note on diagnosis and electromyograms, 138
- Autolysis, behavior of lipids during autolysis of liver and brain, 284
- Aviation and Aviators, neuropsychiatric aspects of aviation medicine, 147
 psychiatric problems in military aviation, 132
- Avitaminoses: See under Vitamins
- Axons: See Neurons
- Babinski Reflex: See under Reflex
- Bailey, P.: Sarcoma of temporal lobe associated with abscess and invading subcutaneous extracranial tissues, 616
- Baker, A. B.: Sequels of equine encephalomyelitis, *398
- Baleham, O. J.: Pathways for pain from stomach of dog, *739
- Barbital and Barbital Derivatives, sodium amylal experiments; further observations, 287
 Therapy: See Mental Diseases
- Barker, L. F.: Acute syphilitic anterior poliomyelopathic syndrome; report of case, *118
- Barnacle, C. H.: Fatalities following electric convulsive therapy; report of 2 cases with autopsy, *107
- Barré-Guillain Syndrome: See Nerves, roots
- Bartemeier, L. H.: Psychiatric study of man with convulsive disorder, 928
- Basedow's Disease: See Goiter, exophthalmic
- Basophilism (Cushing): See under Pituitary Body
- Beaton, L. E.: Neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- Behavior, Animal: See Psychology, comparative
- Children's: See under Children
- Bell's Palsy: See Paralysis, facial
- Bender, M. B.: Functional representation in oculomotor and trochlear nuclei, *98
- Bennett, A. E.: Myasthenia gravis; curare sensitivity; new diagnostic test and approach to causation, *537
- Berger Rhythm: See Brain, electroencephalography
- Blohn: See Vitamins, B
- Black, H. A.: Intracranial epidermoids occurring simultaneously below and above tentorium, *214
- Bladder, neurogenic vesical dysfunction, 602
- Blakeslee, G. A.: President's address; neuropsychiatry in wartime, 773
- Blast: See Explosions
- Blastomyces hominis; new staining method for demonstration of Debaryomyces neoformans (Torula histolytica), Blastomyces hominis, Coecidioides immitis and Histoplasma capsulatum in histologic preparations, 621
- Blindness: See Vision, defective
 Word Blindness: See Aphasia
- Blood: See also Hemoglobin and Hemoglobin Compounds
 arterial and cerebral venous blood, 466
 arterial and cerebral venous blood; arterial-venous differences in man, 284
 bromide; value of bromide determinations in diagnosis and treatment of bromide intoxication, 128
 chemical changes in blood and occurrence of uremia following head injury, 467
 distribution of iodine in blood serum and in spinal fluid, *93
 lactic acid; blood lactate-pyruvate relation and its use in experimental thiamine deficiency in pigeons, 127
 pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional instability, 915
 pressure high; arterial hypertension following metrazol shock therapy, *120
 pressure, high; chronic hypertensive encephalopathy; clinicopathologic report, 919
 pyruvic acid; blood lactate-pyruvate relation and its use in experimental thiamine deficiency in pigeons, 127
 Sugar: See also Dextrose; Insulin; etc.
 sugar; effect on electroencephalogram of changing blood sugar level, *186
 sugar in case of complete hypophysectomy, 136
 sugar; interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
 sugar; observations in hypoglycemia; spinal fluid sugar and coma, 287
 sugar; oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis, *852
 sugar; sodium amylal experiments; further observations, 287
- Bones: See also under names of bones
 atrophy; roentgenographic appearance of bones in Cushing's syndrome, 613
- BOOK REVIEWS:
 Autonomic Regulation; E. Gellhorn, 792
 Biologic Fundamentals of Radiation Therapy; F. Ellinger, 322
 Conceptual Thinking in Schizophrenia; E. Hanfmann and J. Kasanin, 321
 Dark Legend: Study in Murder; F. Wertham, 930
 Encephalography; E. G. Robertson, 487
 Introduction to Psychoanalytic Theory of Libido; R. Sterba, 639
 Lectures on Conditioned Reflexes: Volume II. Conditioned Reflexes and Psychiatry; I. P. Pavlov, 637
 Love Against Hate; K. Menninger, with collaboration of J. L. Menninger, 638
 Mental Health in College; C. C. Fry, with collaboration of E. G. Rostow, 638
 Mental Illness: Guide for Family; E. M. Stern and S. W. Hamilton, 488
 Our Age of Unreason; F. Alexander, 639
 Psychology You Can Use; W. H. Roberts, 930
 Roentgen Treatment of Diseases of Nervous System; C. Dyke and L. Davidoff, 930
 Rorschach Technique: Manual for Projective Method of Personality Diagnosis; B. Klopfer and D. Kelley, 930

Book Reviews—Continued

- Sex Guidance in Family Life Education; F. B. Strain, 150
- Text-Book of Neuro-Anatomy; A. T. Kuntz, 488
- Unconsciousness; J. G. Miller, 320
- Visual Mechanisms; edited by H. Kluver, 150
- Boyd, D. A., Jr.: Encephalopathy following intravenous administration of arsenical preparations, *863
- Brachial Plexus: See Paralysis
- Brain: See also Cerebrum; Corpus Callosum; Hypothalamus; Lenticular Nucleus; Medulla Oblongata; Meninges; Nervous System; Pons Varolii; Thalamus; etc.
- abnormalities: cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
- abscess; treatment, 612
- atypical seizures elicited by electrical stimulation of cerebrum in cat, *211
- behavior of lipids during autolysis of liver and brain, 284
- Blood Supply: See also Aneurysm; Arteries; Arteriosclerosis; etc.
- blood supply; arterial and cerebral venous blood, 466
- blood supply; arterial and cerebral venous blood: arterial-venous differences in man, 281
- blood supply; effect of alkalosis and acidosis on cortical electrical activity and blood flow, 286
- blood supply; fatal cerebrovascular accident associated with catatonic schizophrenia; report of case, *721
- blood supply; histogenesis of early lesions of multiple sclerosis; significance of vascular changes, *178
- blood supply; military aneurysms; relation of anomalies of circle of Willis to formation of aneurysms, 615
- calcification of cerebral cortex associated with meningiotheliomatous meningioma; pathologic study, with comment on incomplic types of neurocutaneous syndrome, *507
- cerebral cortex in groundhog (*Marmota monax*) and deer mouse (*Peromyscus maniculatus*), 164
- cerebral dysrhythmia in relation to eclampsia, *204
- control of clonic responses of cerebral cortex, 921
- cortical premotor and "postmotor" foci which influence gastrointestinal tract and their efferent pathways, 485
- cytoarchitectural study of sheep cortex, 461
- Diseases: See also Encephalitis; Insanity; Mental Diseases; etc.
- diseases; chronic hypertensive encephalopathy; clinicopathologic report, 919
- diseases; encephalopathy following intravenous administration of arsenical preparations, *863
- edema; effect of hypertonic glucose solutions on inflow of normal saline solution into subarachnoid space of dog, 467
- edema; experimental swelling of brain, *826
- effect of cortical destruction on responses to tones, 127
- electroencephalogram in Addison's disease, 137
- electroencephalogram in "convulsive state," 600
- electroencephalogram in epilepsy, 296
- electroencephalographic foci associated with epilepsy, *793
- electroencephalographic studies in delinquent behavior problem children, 130
- electroencephalographic studies of psychopathic personalities, 916
- electroencephalography; changes in normal electroencephalogram of *Macaca mulatta* with growth, 601
- Brain—Continued
- electroencephalography; delinquency and electroencephalography, 130
- electroencephalography; effect on electroencephalogram of changing blood sugar level, *186
- electroencephalography; effect on electroencephalogram of lesions of cerebral cortex and basal ganglia in *Macaca mulatta*, 601
- electroencephalography in cases of mental disorder, 292
- electroencephalography; potentials and morphine addiction, 915
- electroencephalography; potentials of rapid frequency in human electroencephalogram, 308
- electroencephalography; significance of abnormal electroencephalogram, 128
- experimental studies on electric shock treatment; intracerebral vascular reaction as indicator of path of current, 617
- formation of demyelinated plaques associated with cerebral fat embolism in man, *754
- function of frontal lobe in man; dynamic visual field, 633
- grouping behavior of normal persons and of persons with lesions of brain; further analysis, *189
- Hemorrhage: See Encephalitis, hemorrhagic
- hernia; acquired subtentorial pressure diverticulum of cerebral lateral ventricle, 613
- histogenesis of cerebral arteriosclerosis, 622
- Inflammation: See Encephalitis
- Injuries: See Head, injuries
- interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
- juvenile amaurotic idioey; clinicopathologic study, *559
- localization of function; interference factors in delayed response in monkeys after removal of frontal lobes, 287
- midbrain deafness; tumor of midbrain producing sudden and complete deafness, *237
- neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- neuropsychiatric sequelae of partial exsanguination, *591
- pathologic changes in brains of dogs given repeated electrical shocks, 602
- pathology; effect on electroencephalogram of lesions of cerebral cortex and basal ganglia in *Macaca mulatta*, 601
- pathology; encephalomalacia with cavity formation in infants, 288
- pathology; Lissauer's dementia paralytica, 601
- Physiology: See also Brain, electroencephalography; Brain, localization of function
- physiology; autonomic responses to electrical stimulation of forebrain and midbrain with reference to pupils, 466
- physiology; studies on metabolism of brain suspensions; oxygen uptake, 911
- presence and localization of vitamin C in central nervous system, 283
- primacy of area 13 of orbital surface of cerebral cortex in production of hyperactivity in monkeys, 780
- pyramidal and extrapyramidal mechanisms in cortical control of movement, 782
- pyramidal tract; effect of precentral and postcentral cortical lesions on fiber components of pyramids in monkey, 285
- sarcoma of temporal lobe associated with abscess and invading subcutaneous extracranial tissues, 616
- Sclerosis: See Sclerosis
- Softening: See Brain, pathology
- surgery; aphasia after major temporal lobectomy, 465
- surgery; investigation of personality in patients treated by prefrontal leukotomy, 292
- surgery; reports of partial frontal lobectomy and frontal lobotomy performed on 3 patients, 473

- Brain—Continued**
 surgery; results of lobotomies at Delaware State Hospital, 139
 surgery; study of frontal lobotomy; neurosurgical and psychiatric features and results in 22 cases with detailed report on 5 chronic schizophrenics, 290
 tumors, early symptoms of aphasia with, 609
 tumors; meningioma, 605
 tumors; narcolepsy, 609
 tumors; successful operation on 3 intracranial cholesteatomas, 139
 tumors; vascularization of cerebral neoplasms studied with fuchsin staining method of Eros, 626
- Bray, D.:** Sibling deaths in anamneses of schizophrenic patients, *71
- Broder, S. B.:** Dr. H. Douglas Slinger's concept of psychoses, *732
- Bromide and Bromine,** predisposing factors in bromide intoxication, *359
 value of bromide determinations in diagnosis and treatment of bromide intoxication, 128
- Brown, M.:** Constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49
- Bucy, P. C.:** Unusual complication of intraspinal use of iodized poppyseed oil, 926
- Cachexia:** See Appetite
- Calcification:** See Brain
- Cancer:** See Sarcoma; Tumors; etc.; and under names of organs and regions
- Capillaries,** constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49
- Carbohydrates:** See Dextrose; etc.
- Cardiazol:** See Dementia Praecox; Metrazol
- Cardiovascular System:** See Arteries; Heart; etc.
- Carotid Sinus,** observations and surgical aspects of carotid sinus reflex in man, 469
- Cash, P. T.:** Myasthenia gravis; eurare sensitivity; new diagnostic test and approach to causation, *537
- Catatonia:** See Dementia Praecox
- Cauda Equina:** See Spinal Cord
- Causalgia:** See Neuralgia
- Cells:** See also Neurons; Tissue; etc.
 inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, *708
- Staining:** See Stains and Staining
- Cephalalgia:** See Headache
- Cephalocele:** See Brain, hernia
- Cerebellum,** atypical seizures elicited by electrical stimulation of cerebellum in cat, *244
 cerebellar action potentials in response to stimulation of proprioceptors and exteroceptors in rat, 601
 circumscribed arachnoid sarcoma of, 289
 functions of, 128
 hereditodegenerative disorders, 610
Localization of Function: See Brain, localization of function
 origin, conduction and termination of impulses in dorsal spinocerebellar tracts (Fleischig's tract) of cats, 286
- Cerebrospinal Fluid:** See also Spinal Puncture
 creatine content of, 294
 distribution of iodine in blood serum and in spinal fluid, *93
 effect of autonomic drugs on spinal fluid pressure in schizophrenic and other psychoses; effect of histamine, *449
 effect of hypertonic glucose solutions on inflow of normal saline solution into subarachnoid space of dog, 467
 electrophoretic study of concentrated spinal fluid, 481
 lumbar and cisternal spinal fluid; normal variation, 294
 observations in hypoglycemia; spinal fluid sugar and coma, 287
- Cerebrospinal Fluid—Continued**
 proteins, group of dementia praecox patients with increase of, 293
 proteins; permanent damage to nervous system following attack of polyradiculoneuritis (Guillain-Barré syndrome): report of case, with necropsy, *895
 proteins; subacute ascending polyradiculoneuritis with albuminocytologic dissociation, 135
 proteins; vestibular functions in Guillain-Barré syndrome, 470
- Cerebrum:** See Brain
- Cervitamic Acid:** See Ascorbic Acid
- Charcot's Disease:** See Sclerosis, amyotrophic lateral
- Charcot-Marie-Tooth Disease:** See Atrophy, muscular
- Chemotherapy:** See Meningitis; Neurosyphilis; etc.
- Children:** See also Infants; etc.
 pseudojacksonian epilepsy in, *223
 reactions of people to war, 140
- Choked Disk:** See Neuritis, optic
- Cholesteatoma, Intracranial epidermoids occurring simultaneously below and above tentorium, *214**
 successful operation on 3 intracranial cholesteatomas, 139
- Choline and Choline Derivatives,** cholinergic nature of nerves to electric organ of torpedo, 468
 relation of fibrillation to acetylcholine and potassium sensitivity in denervated skeletal muscle, 467
- Circle of Willis:** See Brain, blood supply
- Circumovary Fascicles:** See Pyramidal Tract
- Clark, S. L.:** Atypical seizures elicited by electrical stimulation of cerebrum in cat, *244
- Coccidioides immitis;** new staining method for demonstration of *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and *Histoplasma capsulatum* in histologic preparations, 621
- Cochlea:** See Ear, internal
- Coma:** See Dementia Praecox; Insulin; etc.
- Communicable Diseases:** See Meningitis; Syphilis; etc.
- Congress:** See Societies
- Constitution;** constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49
- Contusions:** See Head, injuries
- Convulsions:** See also Epilepsy; Epilepsy
 atypical seizures elicited by electrical stimulation of cerebrum in cat, *244
 interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
 modified Rorschach technic for description of transitory postconvulsive personality states, 290
- Corpus Callosum,** lipoma of, 289
 studies on; relationship of grasp reflex to section of corpus callosum, *820
- Corpus Luysi:** See Hypothalamus
- Restiforme:** See under Medulla Oblongata
- Corticospinal Tract:** See Pyramidal Tract
- Cotton,** foreign body granulomas produced by surgical cotton, *581
- Cowden, F. E.:** Atypical seizures elicited by electrical stimulation of cerebrum in cat, *244
- Cranium:** See also Head; Occipital Bone
 experimental studies on headache; analysis of headache associated with changes in intracranial pressure, *323
 fractures; traumatic hemorrhage into pituitary gland, 603
 injuries: See Head, injuries
 intracranial dermoid and epidermoid tumors, *56
 intracranial epidermoids occurring simultaneously below and above tentorium, *214
 sarcoma of temporal lobe associated with abscess and invading subcutaneous extracranial tissues, 616

- Crawford, A. S.: Diagnosis and surgical pathology of certain types of sciatic neuritis, 928
- Creatine and Creatinine, in Cerebrospinal Fluid: See under Cerebrospinal Fluid
- studies in diseases of muscle; progressive muscular dystrophy of atrophic distal type; report on family; report of autopsy, *655
- Cresyl Phosphates, systemic nervous affinity of triorthocresyl phosphate (jamalca ginger palsy), 470
- Crime and Criminals: See also Delinquency; Jurisprudence, Medical; Suicide; etc.
- masochistic motives in criminal behavior, 630
- Medical Correctional Association, 771
- value of formal psychiatric examinations in criminal court, 629
- Crothers, B.: Toxoplasmic encephalitis; clinical experience, 315
- Culture, acculturation processes and personality changes as indicated by Rorschach technic, 131
- Curare, myasthenia gravis; curare sensitivity; new diagnostic test and approach to causation, *537
- Cushing's Syndrome: See Pituitary Body
- Cysts: See under names of organs and regions, as Spine; etc.
- Davis, E. W.: Gliomatous tumors in nasal region, 625
- Davis, L.: Intracranial dermoid and epidermoid tumors, *56
- Davis, P. A.: Effect on electroencephalogram of changing blood sugar level, *186
- Davison, C.: Effect of vitamin E therapy on central nervous system in amyotrophic lateral sclerosis, 778
- Paraphenylenediamine poisoning with changes in central nervous system, *254
- Deafness: See also Ear
- midbrain deafness; tumor of midbrain producing sudden and complete deafness, *237
- Death, analysis of deaths following therapeutic malaria, 611
- sibling deaths in anamneses of schizophrenic patients, *71
- Debaryomyces Neoformans: See Torula
- Degeneration, Hepatolenticular: See Lenticular Nucleus, degeneration
- retrograde; effect of hemisections on homolateral axons of spinal cord, *878
- Dehne, T. L.: Symposium; complications of and contraindications to electric shock therapy, 786
- De Jong, R. N.: Syndrome of involvement of posterior cord of brachial plexus, *860
- Delinquency and electroencephalograph, 130
- electroencephalographic studies in delinquent behavior problem children, 130
- DeLury, D. B.: Effect of electrical stimulation on atrophy of denervated skeletal muscle, *802
- Delusions: See under Dementia Praecox; Insanity; etc.
- Dementia: See Dementia Paralytica; Dementia Praecox; Insanity; etc.
- Presenile: See Insanity, presenile
- Dementia Paralytica: See also Neurosyphilis
- Lissauer's, 604
- Dementia Praecox, attempts at treatment of schizophrenia and other nonepileptic psychoses with diltantin, *414
- catatonic pupils, 918
- comparison of metrazol convulsive therapy with electric shock in treatment of schizophrenia; evaluation of results obtained in treatment of 100 schizophrenic patients with electric shock, *587
- Dr. H. Douglas Singer's concept of psychoses, *732
- effect of autonomic drugs on spinal fluid pressure in schizophrenic and other psychoses; effect of histamine, *449
- experimental and clinical studies with methylguanidine sulfate, 145
- Dementia Praecox—Continued
- fatal cerebrovascular accident associated with catatonic schizophrenia; report of case, *724
- group of dementia praecox patients with increase of protein content of spinal fluid, 293
- hyperthyrotic catatonia; schizophrenic symptom-complex, 291
- psychosis associated with progressive muscular dystrophy, 307
- report of family exhibiting hereditary mirror movements and schizophrenia, 913
- results of insulin and epinephrine tolerance tests in schizophrenic patients and in normal subjects, *195
- schizophrenic language, *831
- sibling deaths in anamneses of schizophrenic patients, *71
- study of frontal lobotomy; neurosurgical and psychiatric features and results in 22 cases with detailed report on 5 chronic schizophrenics, 290
- symposium; complications of and contraindications to electric shock therapy, 786
- treatment of schizophrenia; follow-up results in cases of insulin shock therapy and in control cases, *266
- use of adrenal cortex extract in cases of insulin shock complicated by pulmonary edema; review of literature and report of case, 304
- Denker, P. G.: Aberrant thyroid tumor of vertebrae with compression of spinal cord; recovery after operation and high voltage roentgen therapy, *277
- Early laminectomy for injury of spinal cord, 773
- Depersonalization: See Personality
- Depression: See also Insanity; Mental Diseases; Neuroses and Psychoneuroses
- successful treatment of case of acute hysterical depression by return under hypnosis to critical phase of childhood, 607
- Dextrose: See also Blood sugar
- effect of hypertonic glucose solutions on inflow of normal saline solution into subarachnoid space of dog, 467
- oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis, *852
- Diabetes Insipidus, inheritance of, 609
- Diamond, B. L.: Clinical evaluation of mosaic test, 478
- Diencephalon: See Brain
- Diethelm, O.: Psychopathologic review of senile and arteriosclerotic disorders, 299
- Diltantin: See Dementia Praecox; Mental Diseases; etc.
- Diplegia: See Paralysis
- Dipsomania: See Alcoholism
- Disk, Choked: See Neuritis, optic
- Intervertebrai: See under Spine
- DI Alpha Tocopherol: See Vitamins, E
- Drugs, Addiction: See also under names of drugs, as Morphine; Paraldehyde; etc.
- addiction; drugs and mental disease, 293
- Dyer, C. G.: Results of insulin and epinephrine tolerance tests in schizophrenic patients and in normal subjects, *195
- Dyes: See also Stains and Staining; etc.
- paraphenylenediamine poisoning (ursol) with changes in central nervous system, *254
- Dysacusia: See Deafness
- Dystrophy, Muscular: See also Atrophy, muscular
- muscular; muscle changes in myopathies and dystrophia myotonica, 474
- muscular; psychosis associated with progressive muscular dystrophy, 307
- muscular; some new applications of synthetic vitamin E therapy, 472
- muscular; studies in diseases of muscle; heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course, *641

Dystrophy—Continued

- muscular; studies in diseases of muscle; progressive muscular dystrophy of atrophic distal type; report on family; report of autopsy, *655
- muscular; use of alpha tocopherol in treatment of neuromuscular disorders, 611

Ear: See also Deafness

- internal; vestibular functions in Guillain-Barré syndrome, 470

Eaton, L. M.: Myasthenia gravis; treatment and relation to thymus, 476

Ebaugh, F. G.: Fatalities following electric convulsive therapy; report of 2 cases with autopsy, *107

Echlin, F. A.: Electroencephalogram in epilepsy, 296

Eclampsia, cerebral dysrhythmia in relation to, *204

Edema: See under names of organs and regions, as Brain; Lungs; etc.

Electroencephalogram: See Brain, electroencephalography

Electromyogram: See under Muscles

Electrophoresis: See Cerebrospinal Fluid

Electrotherapy: See also under Dementia Praecox; Mental Diseases; etc.

atypical seizures elicited by electrical stimulation of cerebrum in cat, *244

comparison of metrazol convulsive therapy with electric shock in treatment of schizophrenia; evaluation of results obtained in treatment of 100 schizophrenic patients with electric shock, *587

effect of electrical stimulation on atrophy of denervated skeletal muscle, *802

electrical skin resistance technic used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454

experimental studies on electric shock treatment; intracerebral vascular reaction as indicator of path of current, 617

fatalities following electric convulsive therapy; report of 2 cases with autopsy, *107

interaction of electric shock and insulin hypoglycemia; experimental investigations, *808

pathologic changes in brains of dogs given repeated electrical shocks, 602

subconvulsive electric shock therapy; effect of varied electrode applications, 302

symposium; complications of and contraindications to electric shock therapy, 786

Embolism: See also Thrombosis

formation of demyelinated plaques associated with cerebral fat embolism in man, *754

Emotions, blood pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional instability, 915

emotional settings of some attacks of urticaria, 914

Encephalitis: See also Encephalomyelitis

associated with herpes zoster; report of case, 633

hemorrhagic; cerebral lesions following administration of neoarsphenamine, 603

toxoplasmic; clinical experience, 315

Encephalocele: See Brain, hernia

Encephalomalacia: See Brain, pathology

Encephalomyelitis, equine, sequels of, *398

scarlatinal, 619

Encephalopathy: See Brain, diseases

Endocrine Therapy: See under names of glands and hormones, as Adrenal Preparations; Insulin

English, O. S.: Ideation and trends encountered in psychotherapy of manic-depressive psychosis, 142

Environment, effect of extremes of environmental change on man; president's address, *421

psychoneuroses of war, 924

Bonism: See Sex, perversion

Epidermoid: See under Cranium

Epilepsy: See also Convulsions

cerebral dysrhythmia in relation to eclampsia, *204

constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49

control of clonic responses of cerebral cortex, 921

deterioration of patients with organic epilepsy, 605

electroencephalogram in, 296

electroencephalogram in "convulsive state," 600

electroencephalographic foci associated with, *793

frequency of convulsive disorders in feeble-minded; clinical and pathoanatomic considerations, 929

modified Rorschach technic for description of transitory postconvulsive personality states, 290

myoclonus epilepsy; clinicopathologic report of case, 627

potentials of rapid frequency in human electroencephalogram, 308

pseudojacksonian, in children, *223

psychiatric study of man with convulsive disorder, 928

reports of partial frontal lobectomy and frontal lobotomy performed on 3 patients, 473

studies on corpus callosum; relationship of grasp reflex to section of corpus callosum, *820

Epinephrine: See Adrenal Preparations

Equilibrium: See Cerebellum; Ear, internal; Posture; etc.

Ergotamine Tartrate: See Headache

Eros, G.: Histogenesis of cerebral arteriosclerosis, 622

Explosions, effect of extremes of environmental change on man; president's address, *421

psychiatric syndromes following blast, 292

Extrapyramidal Tract: See also Lenticular Nucleus

pyramidal and extrapyramidal mechanisms in cortical control of movement, 782

Extremities: See also Arms

Paralysis: See also Poliomyelitis

paralysis; cure of paralysis in rats with biotin concentrates and crystalline biotin, 285

preganglionic components of first thoracic nerve; their role in sympathetic innervation of upper extremity, 126

sympathetic denervation of feet and leg occurring spontaneously or as result of disease, 126

Extroversion: See under Personality

Eyes: See also Orbit; Vision; and under special structures of eyes

changes in amaurotic family idiocy (infantile type of Tay-Sachs disease); histopathologic observations in case, 629

muscles; functional representation in oculomotor and trochlear nuclei, *98

paralysis; frequency, etiology and prognosis of eye muscle palsies, 295

Face, experiences with intramedullary tractotomy; immediate and late neurologic complications, *665

Paralysis: See Paralysis, facial

Fantopias: See Hallucinations

Faradic Shock: See Mental Diseases

Fat: See Lipoids

Fatigue, behavior of motor units in healthy and in parietic muscles in man, 129

effect of extremes of environmental change on man; president's address, *421

Feeble-mindedness: See also Idiocy

frequency of convulsive disorders in feeble-minded; clinical and pathoanatomic considerations, 929

Ferraro, A.: Histogenesis of cerebral arteriosclerosis, 622

Myoclonus epilepsy; clinicopathologic report of case, 627

Fetus, early human fetal movements, 600

- Fever: See also Malaria; etc.
 Artificial: See Neurosyphilis
 neurogenic hyperthermia and its treatment
 with soluble pentobarbital in monkey, *518
 Therapeutic: See under Dementia Paralytica;
 Neurosyphilis; Syphilis; etc.
- Fibrosarcoma of arachnoidal origin with meta-
 stases, 288
- Filum Terminale: See Spinal Cord
- Finger Nail: See Nails
- Finley, K. H.: Potentials of rapid frequency in
 human electroencephalogram, 308
- Flechsig's Tract: See Cerebellum; Spinal Cord
- Foramen, Intervertebral: See under Spine
- Foreign Bodies, foreign body granulomas pro-
 duced by surgical cotton, *581
- Fractures: See Cranium; Spine; etc.
- Freeman, H.: Results of insulin and epin-
 ephrine tolerance tests in schizophrenic
 patients and in normal subjects, *195
- Freeman, W.: Spinal necrosis and softening of
 obscure origin; necrotic myelitis versus
 myelomaia; review of literature and
 clinicopathologic case studies, *683
- Friedman, E.: Effect of autonomic drugs on
 cerebrospinal fluid pressure in schizo-
 phrenic and other psychoses; effect of his-
 tamine, *449
- Friedreich's Disease: See Ataxia
- Frocht, M.: Myasthenia gravis; familial oc-
 currence, *904
- Fuchsian: See Stains and Staining
- Ganglion: See also Gasserian Ganglion
 effect on electroencephalogram of lesions of
 cerebral cortex and basal ganglia in Ma-
 caea mulatta, 601
 experimental verification of differences in
 argyrophilia of sympathetic postganglionics
 and of other nerve fibers, 910
 Nodose: See Neurons
- Ganglionectomy: See Sympathectomy
- Gasserian Ganglion: See also Neuralgia, trige-
 minal
 tumors, and trigeminal neuralgia, 610
- Gastrointestinal Tract: See also Stomach; etc.
 cortical premotor and "postmotor" foci which
 influence gastrointestinal tract and their
 efferent pathways, 485
- Gellhorn, E.: Interaction of electric shock and
 insulin hypoglycemia; experimental inves-
 tigations, *808
- German, W. M.: Foreign body granulomas pro-
 duced by surgical cotton, *581
- Gibbs, E. L.: Electroencephalographic foci as-
 sociated with epilepsy, *793
- Gibbs, F. A.: Electroencephalographic foci
 associated with epilepsy, *793
- Gildea, E. F.: Distribution of iodine in blood
 serum and in cerebrospinal fluid, *93
 Oral and intravenous dextrose tolerance
 curves of patients with manic-depressive
 psychosis, *852
- Glioma; gliomatous tumors in nasal region, 625
 meningeal gliomatosis secondary to intra-
 medullary glioma, *383
- Globus Pallidus: See Lenticular Nucleus
- Glucose: See Dextrose
- Goiter: See also Thyroid
 exophthalmic; hyperthyrotic catatonias; schizo-
 phrenic symptom-complex, 291
 exophthalmic, with associated myasthenia
 gravis, 473
- Goodman, L.: Chronic hypertensive encephalop-
 athy; clinicopathologic report, 919
- Gottesfeld, B. H.: Psychosis associated with
 progressive muscular dystrophy, 307
 Subconvulsive electric shock therapy; effect of
 varied electrode applications, 302
 Use of adrenal cortex extract in cases of
 insulin shock complicated by pulmonary
 edema; review of literature and report of
 case, 304
- Gottlieb, J. S.: Treatment of schizophrenia;
 follow-up results in cases of insulin shock
 therapy and in control cases, *266
- Grain, G. O.: Bilateral ageusia associated with
 unilateral Bell's palsy, 926
- Grant, F. C.: Experiences with intramedullary
 tractotomy; immediate and late neurologic
 complications, *665
 Tumor of cauda equina with unusual onset
 and symptoms; report of case, 479
- Granuloma, foreign body granulomas produced
 by surgical cotton, *581
- Malignant: See Hodgkin's Disease
- Growth, changes in normal electroencephalo-
 gram of *Macaca mulatta* with growth, 601
- Guanidine and Guanidine Compounds: See also
 Creatine and Creatinine
 experimental and clinical studies with methyl-
 guanidine sulfate, 145
- Guillain-Barré Syndrome: See Nerves, roots
- Guttman, S. A.: Treatment of post-lumbar-
 puncture headache with ergotamine tartrate,
 *556
- Hallucinations, visual, during paraldehyde ad-
 diction, 913
- Halstead, W. C.: Function of frontal lobe in
 man; dynamic visual field, 633
 Grouping behavior of normal persons and of
 persons with lesions of brain; further
 analysis, *489
- Hamilton, E. L.: Rorschach method in state
 hospital practice, 306
- Hassin, G. B.: Changes in eyes in amaurotic
 family idiocy (infantile type of Tay-Sachs
 disease); histopathologic observations in
 case, 629
- Hay Fever, study of structural and instinctual
 conflicts in cases of, 607
- Head: See also Cranium
 Injuries: See also Cranium, fractures; etc.
 injuries; chemical changes in blood and oc-
 currence of uremia following head injury,
 467
 injuries; statistical control studies in neu-
 rology; Babinski sign, *272
- Headache, experimental studies; analysis of
 headache associated with changes in in-
 tra-cranial pressure, *323
 treatment of post-lumbar-puncture headache
 with ergotamine tartrate, *556
- Heart, histochemical changes associated with
 aging; skeletal and cardiac muscle in rat,
 912
- Hebephrenia: See Dementia Praecox
- Heine-Medin's Disease: See Poliomyelitis
- Hematoma, Subdural: See Meninges, hemor-
 rhage
- Hemianopia, bilateral thrombosis of posterior
 calcarine arteries with sparing of macular
 vision, 484
 study of, 918
- Hemiplegia: See Extremities, paralysis; Par-
 alysis
- Hemoglobin and Hemoglobin Compounds, normal
 rate of reduction of methemoglobin in dogs,
 284
- Hemorrhage: See also Encephalitis; Pituitary
 Body; etc.
 neuropsychiatric sequelae of partial exsan-
 guination, *594
 Subarachnoid: See Meninges, hemorrhage
- Hernia: See under Brain
- Herpes zoster associated with encephalitis; re-
 port of case, 633
 zoster, symptomatic, 135
- Herskovitz, H. H.: Psychosis associated with
 progressive muscular dystrophy, 307
 Subconvulsive electric shock therapy; effect
 of varied electrode applications, 302
- Hinsey, J. C.: Stephen Walter Ranson, 457
- Hirschfield, B. A.: Spontaneous subarachnoid
 hemorrhage; analysis of 50 cases, 483
- Histamine, effect of autonomic drugs on cere-
 brospinal fluid pressure in schizophrenic
 and other psychoses; effect of histamine,
 *449

- Histoplasma capsulatum*; new staining method for demonstration of *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and *Histoplasma capsulatum* in histologic preparations, 621
- Hodgkin's Disease, *torula meningitis* (in association with Hodgkin's disease), 468
- Hormones: See Adrenal Preparations; Androgens; Insulin; etc.
- Hoskins, R. G.: Results of insulin and epinephrine tolerance tests in schizophrenic patients and in normal subjects, *195
- Hospitals, results of lobotomies at Delaware State Hospital, 139
- Rorschach method in state hospital practice, 306
- ward therapy; new method of group psychotherapy, 611
- Hunter, J.: Effect of electrical stimulation on atrophy of denervated skeletal muscle, *802
- Huston, P. E.: Treatment of schizophrenia; follow-up results in cases of insulin shock therapy and in control cases, *266
- Hydrophobia: See Rabies
- Hyperpyrexia: See Fever
- Hypertension: See Blood pressure, high
- Hyperthermia: See Fever
- Hypertonic Solution: See Brain, edema
- Hypervitaminoses: See Vitamins
- Hypnosis, successful treatment of case of acute hysterical depression by return under hypnosis to critical phase of childhood, 607
- Hypoglycemia: See Blood sugar; insulin
- Hypomania: See Mental Diseases
- Hypophysis: See Pituitary Body
- Hypothalamus: See also Pituitary Body
neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- Idiocy: See also Feeblemindedness
changes in eyes in amaurotic family idiocy (infantile type of Tay-Sachs disease); histopathologic observations in case, 629
inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, *708
juvenile amaurotic; clinicopathologic study, *559
- Imbecility: See Idiocy
- Incest and its effect on participants, 144
- Inebriety: See Alcoholism
- Infantile Paralysis: See Poliomyelitis
- Infants: See also Children
familial type of paralysis in infants and its relationship to other hereditary disorders; clinicopathologic study, *27
- Infundibulum: See Hypothalamus
- Injuries: See Head, injuries; Spinal Cord; etc.
- Insanity: See also Dementia Praecox; Depression; Mental Diseases
- Alcoholic: See Alcoholism
- manic-depressive; Dr. H. Douglas Singer's concept of manic-depressive psychosis, *736
- manic-depressive; ideation and trends encountered in psychotherapy of manic-depressive psychosis, 142
- manic-depressive; nitrogen balance in patients suffering from melancholia, 129
- manic-depressive; oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis, *852
- prescille; calcification of cerebral cortex associated with meningotheiomatous meningioma; pathologic study, with comment on incomplete type of neurocutaneous syndrome, *507
- reports of partial frontal lobectomy and frontal lobotomy performed on 3 patients, 473
- symposium; complications of and contraindications to electric shock therapy, 786
- Instruments: See also Apparatus
disturbances in parotid secretion in unusual neurologic syndrome, *548
- Insulin, interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
results of insulin and epinephrine tolerance tests in schizophrenic patients and in normal subjects, *195
treatment of schizophrenia; follow-up results in cases of insulin shock therapy and in control cases, *266
use of adrenal cortex extract in cases of insulin shock complicated by pulmonary edema; review of literature and report of case, 304
- Intelligence Tests: See Mental Tests
- Intervertebral Disks: See under Spine
- Intoxication: See Alcoholism; Bromide and Bromine
- Introversion: See under Personality
- Iodine and Iodine Compounds, in Blood: See Blood
unusual complication of intraspinal use of iodized poppyseed oil, 926
- Iodized Poppyseed Oil: See Spinal Cord
- Jaffe, D.: Spinal necrosis and softening of obscure origin; necrotic myelitis versus myelomalacia; review of literature and clinicopathologic case studies, *683
- "Jake" Paralysis: See Neuritis, peripheral
- Jamaica Ginger Palsy: See Neuritis, peripheral
- Jeffreys, E. O.: Tumor of cauda equina with unusual onset and symptoms; report of case, 479
- Jones, G. L.: Symposium; complications of and contraindications to electric shock therapy, 788
- Jurisprudence, Medical: See Alcoholism; Crime and Criminals; Suicide; etc.
value of formal psychiatric examinations in criminal court, 629
- Kabat, E. A.: Electrophoretic study of concentrated cerebrospinal fluid, 481
- Kalinowsky, L. B.: Attempts at treatment of schizophrenia and other nonepileptic psychoses with diltantin, *414
- Kaplan, L. A.: Experimental and clinical studies with methylguanidine sulfate, 145
- Kaufman, S. H.: Value of formal psychiatric examinations in criminal court, 629
- Kennedy, F.: Early laminectomy for injury of spinal cord, 773
- Kennedy Syndrome: See Neuritis, optic
- Kenny Method: See Poliomyelitis
- Kerman, E. F.: Testosterone therapy of involutional psychosis, 306
- Kernohan, J. W.: New staining method for demonstration of *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and *Histoplasma capsulatum* in histologic preparations, 621
- Kessler, M.: Interaction of electric shock and insulin hypoglycemia; experimental investigations, *808
- Krumholz, S.: Encephalitis associated with herpes zoster; report of case, 633
- Kunkle, E. C.: Experimental studies on headache; analysis of headache associated with changes in intracranial pressure, *323
- Labyrinth: See Ear, internal
- Laminectomy: See under Spinal Cord
- Landow, H.: Electrophoretic study of concentrated cerebrospinal fluid, 481
- Landry's Paralysis: See Paralysis, acute ascending
- Language, schizophrenic, *831
- Lassek, A. M.: Retrograde degeneration; effect of hemisections on homolateral axons of spinal cord, *878
- Lehninger, C.: Neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- Lenticular Nucleus, degeneration; characteristic alterations in ganglion cells in cases of hepatolenticular degeneration and other hepatocerebral diseases, 289
- Lesse, S.: Subconvulsive electric shock therapy; effect of varied electrode applications, 302

- Leukotomy: See Brain, surgery
- Lev, M.: Calcification of cerebral cortex associated with meningotheioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
- Lichtenstein, B. W.: Calcification of cerebral cortex associated with meningotheioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
- Cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
- Lindau's Disease: See Angioma
- Lindenfeld, A.: Symposium; complications of and contraindications to electric shock therapy, 787
- Linn, L.: Disturbances in parotid secretion in unusual neurologic syndrome, *548
- Lipids: See Lipoids
- Lipiodol: See Spinal Cord
- Lipoids: See also Phosphorus and Phosphorus Compounds
- behavior of lipids during autolysis of liver and brain, 284
- study of nitrogenous constituents of tissue phosphatides, 285
- Lipoma of corpus callosum, 289
- Lissauer's Paralysis: See Dementia Paralytica
- Liver, behavior of lipids during autolysis of liver and brain, 284
- cirrhosis and vitamin deficiencies in alcoholism, 135
- cirrhosis, experimental, effect of alcohol in, 467
- Lobectomy: See Brain, surgery
- Lototomy: See Brain, surgery
- Looney, J. M.: Results of insulin and epinephrine tolerance test in schizophrenic patients and in normal subjects, *195
- Louping III: See Encephalomyelitis
- Lowenbach, H.: Experimental studies on electric shock treatment; intracerebral vascular reaction as indicator of path of current, 617
- Lubin, A. J.: Familial type of paralysis in infants and its relationship to other hereditary disorders; clinicopathologic study, *27
- Juvenile amaurotic idiocy; clinicopathologic study, *559
- Luhan, J. A.: Encephalitis associated with herpes zoster; report of case, 633
- Lumbar Puncture: See Spinal Puncture
- Lungs: See also Respiration; etc.
- edema; use of adrenal cortex extract in cases of insulin shock complicated by pulmonary edema; review of literature and report of case, 304
- Lymphogranuloma, Hodgkin's: See Hodgkin's Disease
- McDonald, P. R.: Bilateral thrombosis of posterior calcarine arterioles with sparing of macular vision, 484
- McKinley, W. A.: Afferent trigeminal pathways as determined by evoked potentials, 475
- Neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- McLean, V. L.: Oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis, *852
- Madden, J. J.: Experimental and clinical studies with methylguanidine sulfate, 145
- Madoniek, M. J.: Statistical control studies in neurology; Babinski sign, *272
- Maeder, L. M. A.: Relations of psychoanalysis to psychiatry, 140
- Magoun, H. W.: Afferent trigeminal pathways as determined by evoked potentials, 475
- Neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- Malaria, analysis of deaths following therapeutic malaria, 611
- Therapeutic: See Dementia Paralytica; etc.
- Malnutrition: See Dystrophy; Vitamins; etc.
- Maltby, G. L.: Cerebral dysrhythmia in relation to eclampsia, *204
- Man, E. B.: Distribution of iodine in blood serum and in cerebrospinal fluid, *93
- Oral and intravenous dextrose tolerance curves of patients with manic-depressive psychosis, *852
- Mania: See Insanity
- Marburg, O.: Familial type of paralysis in infants and its relationship to other hereditary disorders; clinicopathologic study, *27
- Inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, *708
- Juvenile amaurotic idiocy; clinicopathologic study, *559
- Marie-Charcot Disease: See Atrophy, muscular
- Martin, J.: Intracranial dermoid and epidermoid tumors, *56
- Masochism: See Sex, perversion
- Masserman, J. H.: Experimental neuroses and psychotherapy, *43
- Mayfield, F. H.: Foreign body granulomas produced by surgical cotton, *581
- Medicine, Military: See Military Medicine
- Medulla Oblongata, experiences with intramedullary tractotomy; immediate and late neurologic complications, *665
- experimental swelling of brain, *826
- meningeal gliomatosis secondary to intramedullary glioma, *383
- Melrowsky, A. M.: Surgical history of trigeminal neuralgia, *574; correction, 791
- Melancholia: See Insanity, manic-depressive
- Involutional: See Mental Diseases
- Meninges: See also Arachnoid
- calcification of cerebral cortex associated with meningotheioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
- fibrosarcoma of arachnoidal origin with metastases, 288
- hemorrhage, spontaneous subarachnoid; analysis of 50 cases, 483
- meningeal gliomatosis secondary to intramedullary glioma, *383
- Meningioma, calcification of cerebral cortex associated with meningotheioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
- Meningitis, prognosis of pneumococcal meningitis treated with chemotherapy, 468
- torula meningitis (in association with Hodgkin's disease), 468
- Meningococci: See under Meningitis
- Menninger, W. C.: Arterial hypertension following metrazol shock therapy, *120
- Mental Deficiency: See Feeble-mindedness
- Mental Diseases: See also Children; Dementia Paralytica; Dementia Praecox; Feeble-mindedness; Insanity; Neuroses and Psychoneuroses; Personality; Psychiatry; etc.
- alcoholism and mental disorder, 608
- alcoholism and mental disorder in Massachusetts, 1917-1933, 131
- and drugs, 293
- arterial hypertension following metrazol shock therapy, *120
- attempts at treatment of schizophrenia and other nonepileptic psychoses with dilantin, *414
- cachexia of mental origin; nature and management, 300
- Dr. H. Douglas Singer's concept of psychoses, *732
- effect of autonomic drugs on spinal fluid pressure in schizophrenic and other psychoses; effect of histamine, *449
- electroencephalogram in "convulsive state," 600
- electroencephalography in cases of mental disorder, 292
- ecstasy; report of case with additional outstanding psychopathic features, 635

Mental Diseases—Continued

- experimental and clinical studies with methylguanidine sulfate, 145
 fatalities following electric convulsive therapy; report of 2 cases with autopsy, *107
 investigation of personality in patients treated by prefrontal leukotomy, 292
 myasthenia gravis and psychosis, 914
 neuropsychiatric sequelae of partial exsanguination, *594
 predisposing factors in bromide intoxication, *359
 prognostic factors of adolescent psychoses, 292
 prognostic possibilities of Rorschach method in metrazol therapy, 927
 psychiatric syndromes following blast, 292
 psychopathology of ego system, 606
 results of lobotomies at Delaware State Hospital, 139
 significance of vertebral fractures as complication of metrazol therapy, 612
 sodium amytal experiments; further observations, 287
 study of frontal lobotomy; neurosurgical and psychiatric features and results in 22 cases with detailed report on 5 chronic schizophrenics, 290
 subconvulsive electric shock therapy; effect of varied electrode applications, 302
 survey of results of intelligence tests in psychosis, 291
 symposium; complications of and contraindications to electric shock therapy, 786
 testosterone therapy of involutional psychosis, 306
- Mental Tests:** See also Personality
 acculturation processes and personality changes as indicated by Rorschach technic, 131
 application of Rorschach test to Samoan group, 603
 clinical evaluation of mosaic test, 478
 course of study in Rorschach test in diagnosis of milder mental disorders, 599
 deterioration of patients with organic epilepsy, 605
 grouping behavior of normal persons and of persons with lesions of brain; further analysis, *489
 modified Rorschach technic for description of transitory postconvulsive personality states, 290
 prognostic possibilities of Rorschach method in metrazol therapy, 927
 psychiatry in war, 923
 psychopathologic review of senile and arteriosclerotic disorders, 299
 relation between blot and concept in graphic Rorschach responses, 131
 Rorschach method in state hospital practice, 306
 survey of results of intelligence tests in psychosis, 291
- Merritt, H. H.: Electroencephalographic foci associated with epilepsy, *793
- Mesencephalon: See Brain
- Methylguanidine Sulfate: See Guanidine and Guanidine Compounds
- Metrazol, arterial hypertension following metrazol shock therapy, *120
 comparison of metrazol convulsive therapy with electric shock in treatment of schizophrenia; evaluation of results obtained in treatment of 100 schizophrenic patients with electric shock, *587
 significance of vertebral fractures as complication of metrazol therapy, 612
- Therapy: See Dementia Praecox; Insanity; Mental Diseases; Neuroses and Psychoneuroses; etc.
- Microglioma, 605
- Micropsia: See Vision, defective
- Milhorat, A. T.: Studies in diseases of muscle; heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course, *641

Milhorat, A. T.—Continued

- Studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
 Studies in diseases of muscle; progressive muscular dystrophy of atrophic distal type; report on family; report of autopsy, *655
- Military Medicine:** See also Aviation and Aviators; Hospitals; Neuroses and Psychoneuroses; Recruits; etc.
 effect of extremes of environmental change on man; president's address, *421
 etiologic factors in adjustment of men in armed forces, 925
 injuries of intravertebral disk in military service, 469
 military psychiatry, 915
 statistical control studies in neurology; Babinski sign, *272
 symposium on military psychiatry, 909
- Mira, E.: Psychiatry in war, 923
- Moore, D. H.: Electrophoretic study of concentrated cerebrospinal fluid, 481
- Moore, W. L.: Permanent damage to nervous system following attack of polyradiculoneuritis (Guillain-Barré syndrome); report of case, with necropsy, *895
- Moro Reflex: See Reflex, grasping
- Morons: See Feeble-mindedness
- Morphine, brain potentials and morphine addiction, 915
- Morris, A. A., Jr.: Apparatus to be used in recording tremors, *123
- Morris, W. W.: Prognostic possibilities of Rorschach method in metrazol therapy, 927
- Mosaic Test: See Mental Tests
- Motoneurons: See Neurons
- Movements: See also Muscles
 Disorders: See Myoclonus; etc.
 pyramidal and extrapyramidal mechanisms in cortical control of movement, 782
 report of family exhibiting hereditary mirror movements and schizophrenia, 913
- Murder: See Crime and Criminals
- Murphy, J. P.: Fatal cerebrovascular accident associated with catatonic schizophrenia; report of case, *724
- Neuropsychiatric sequelae of partial exsanguination, *594
- Muscles, Atrophy: See Atrophy, muscular
 behavior of motor units in healthy and in parietic muscles in man, 129
- Dystrophy: See Dystrophy, muscular
 effect of electrical stimulation on atrophy of denervated skeletal muscle, *802
 fascicular muscle twitches in amyotrophic lateral sclerosis; their origin, *22
 histochemical changes associated with aging; skeletal and cardiac muscle in rat, 912
 muscle changes in myopathies and dystrophies, myotonia, 474
 neuromuscular hypertension and understanding of nervous conditions, 912
- Paralysis: See Paralysis
 potassium and muscular disorders, 294
 relation of fibrillation to acetylcholine and potassium sensitivity in denervated skeletal muscle, 467
- studies in diseases of; heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course, *641
- studies in diseases of; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
- studies in diseases of; progressive muscular dystrophy of atrophic distal type; report on family; report of autopsy, *655
- treatment of certain muscular atrophies with vitamin E with note on diagnosis and electromyograms, 138
- use of alpha tocopherol in treatment of neuromuscular disorders, 611

Myasthenia Gravis and psychosis, 914
 curare sensitivity; new diagnostic test and approach to causation, *537
 familial occurrence, *904
 goltz with associated myasthenia gravis, 473
 potassium and muscular disorders, 294
 treatment and relation to thymus, 476
 Myelin: See under Brain; Nerves; Nervous System
 Myelitis, spinal necrosis and softening of obscure origin; necrotic myelitis versus myelomalacia; review of literature and clinicopathologic case studies, *683
 Myelomalacia: See under Spinal Cord
 Myelopathy: See under Spinal Cord
 Myoclonus epilepsy; clinicopathologic report of case, 627
 oculolaryngopharyngovelopalative myoclonia in bulbopontile syndrome, 604
 Myography: See under Muscles
 Myotonia, Dystrophiea: See Dystrophy, muscular

 Nails, constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49
 Narcolepsy: See Sleep, disturbances
 Necrosis: See Spinal Cord
 Neosphenamine: See Arsphenamines
 Nerves: See also Nervous System; Neuralgia; Neuritis; Paralysis
 Cells: See Neurons
 cerebellar action potentials in response to stimulation of proprioceptors and exteroceptors in rat, 601
 cholinergic nature of nerves to electric organ of torpedo, 468
 experiences with intramedullary tractotomy: immediate and late neurologic complications, *665
 fascicular muscle twitches in amyotrophic lateral sclerosis; their origin, *22
 motor; behavior of motor units in healthy and in paralytic muscles in man, 129
 oculomotor; functional representation in oculomotor and trochlear nuclei, *98
 Optic: See Neuritis, optic
 pathways for pain from stomach of dog, *739
 preganglionic components of first thoracic nerve; their role in sympathetic innervation of upper extremity, 126
 roots; permanent damage to nervous system following attack of polyradiculoneuritis (Guillain-Barré syndrome); report of case, with necropsy, *895
 roots; regenerative capacity of ventral roots after avulsion from spinal cord, *1
 roots; subacute ascending polyradiculoneuritis with albuminocytologic dissociation, 135
 roots; vestibular functions in Guillain-Barré syndrome, 470
 Sciatic: See Sciatica
 Spinal: See Nerves, roots
 structures of neurohypophysis with reference to nerve endings, 283
 studies of living nerves; growth adjustments of cutaneous terminal arborizations, 910
 transplantation of aneurogenic forelimbs in Amblystoma punctatum, 911
 Trigeminal: See also Neuralgia, trigeminal
 trigeminal; afferent trigeminal pathways as determined by evoked potentials, 475
 trochlear; functional representation in oculomotor and trochlear nuclei, *98
 Tumors: See Nervous System
 Nervous System: See also Brain; Cerebellum; Nerves; Neurons; Reflex; Spinal Cord; etc.
 and regeneration of forelimb of adult Triturus; role of sympathetics, 911
 autonomic responses to electrical stimulation of forebrain and midbrain with reference to pupil, 466

Nervous System—Continued
 calcification of cerebral cortex associated with meningotheiomatous meningioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
 cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
 Diseases: See also Epilepsy; Mental Disorders; Neuritis; Neuroses and Psychoneuroses; etc.
 diseases; predisposing factors in bromide intoxication, *359
 disturbances in parotid secretion in unusual neurologic syndrome, *548
 effect of extremes of environmental change on man: president's address, *421
 effect of vitamin E therapy on central nervous system in amyotrophic lateral sclerosis, 778
 familial type of paralysis in infants and its relationship to other hereditary disorders; clinicopathologic study, *27
 in vitro formation of phospholipid by brain and nerve with radioactive phosphorus as indicator, 284
 paraphenylenediamine poisoning (ursol) with changes in central nervous system, *254
 permanent damage following attack of polyradiculoneuritis (Guillain-Barré syndrome); report of case, with necropsy, *895
 sequelae of equine encephalomyelitis, *398
 Surgery: See also Brain, surgery; etc.
 surgery; American Board of Neurological Surgery, 282, 599
 sympathetic denervation of feet and legs occurring spontaneously or as result of disease, 126
 Syphilis: See Neurosyphilis
 Tumors: See Neurofibromatosis; Neuroma; etc.
 war and nervous disturbances, 916
 Nervousness: See Neuroses and Psychoneuroses
 Neuburger, K. T.: Fatalities following electric convulsive therapy; report of 2 cases with autopsy, *107
 Neumann, M. A.: Fatal cerebrovascular accident associated with catatonic schizophrenia; report of case, *724
 Neuralgia, trigeminal, and tumors of gasserian ganglion, 610
 trigeminal; experiences with intramedullary tractotomy; immediate and late neurologic complications, *665
 trigeminal, surgical history of, *574; correction, 791
 Neuritis, diagnosis and surgical pathology of certain types of sciatic neuritis, 928
 optic, following Well's disease, 471
 peripheral; systemic nervous affinity of triorthoethyl phosphate (jamalca ginger palsy), 470
 Neurohypophysis: See Pituitary Body
 Neurology: See also Nerves; Nervous System; Neuropsychiatry; Neuroses and Psychoneuroses; etc.
 statistical control studies in neurology; Babinski sign, *272
 Neurons, characteristic alterations in ganglion cells in cases of hepatolenticular degeneration and other hepatocerebral diseases, 289
 experimental verification of differences in argyrophilia of sympathetic postganglionics and of other nerve fibers, 910
 inclusion bodies and late fate of ganglion cells in infantile amaurotic family idiocy, *708
 retrograde degeneration; effect of hemisections on homolateral axons of spinal cord, *878
 Neuropsychiatry: See also Neurology; Psychiatry; War; etc.
 in wartime; president's address, 773
 neuropsychiatric aspects of aviation medicine, 147
 neuropsychiatric sequelae of partial exsanguination, *594
 School of Military Neuropsychiatry, 771

- Neuroses and Psychoneuroses; See also Mental Diseases; Nervous System, diseases; Phobias; etc.
 Dr. H. Douglas Singer's concept of psychoses, *732
 experimental neuroses and psychotherapy, *43
 incidence of neurosis in cases of bronchial asthma, 914
 neuromuscular hypertension and understanding of nervous conditions, 912
 origin and development of nervous disturbances experimentally produced, 129
 psychoneuroses of war, 924
- Neurosurgery: See Brain, surgery; Nervous System, surgery
- Neurosyphilis: See also Dementia Paralytica
 analysis of deaths following therapeutic malaria, 611
 combined artificial fever, chemotherapy and vaccine therapy in treatment, 472
 juvenile, artificial fever therapy, 138
 management of, 471
- Nicotinic Acid: See also Vitamins, B
 deficiency studies in dogs, 466
- Nie, L.: Encephalopathy following intravenous administration of arsenical preparations, *863
- Nitrogen balance in patients suffering from melancholia, 129
 study of nitrogenous constituents of tissue phosphatides, 285
- Noran, H. H.: Sequels of equine encephalomyelitis, *398
- Nose: See also Smell; etc.
 gliomatous tumors in nasal region, 625
- Nucleus Lateralis Medullae: See Medulla Oblongata
- Pulposus: See Spine, intervertebral disks
- Nutrition: See also Dystrophy; Vitamins
 predisposing factors in bromide intoxication, *359
- Obituaries:**
 Ranson, Stephen Walter, 457
- Obrador, S.: Experimental swelling of brain, *826
- Obsessions: See Neuroses and Psychoneuroses
- Occipital Bone, cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
- Oil, Iodized: See Iodine and Iodine Compounds
- Old Age, psychopathologic review of senile and arteriosclerotic disorders, 299
- Olfactometry: See under Smell
- Oligophrenia: See Feeble-mindedness; Idiocy
- Olivary Body: See Medulla Oblongata
- Olkon, D. M.: Etonism; report of case with additional outstanding psychopathic features, 635
- Ophthalmoplegia: See Eyes, paralysis
- Oppenheimer, M. J.: Cortical premotor and "postmotor" foci which influence gastrointestinal tract and their efferent pathways, 485
- Optic Disk, Choked: See Neuritis, optic
- Optic Thalamus: See Thalamus
- Orbit, primacy of area 13 of orbital surface of cerebral cortex in production of hyperactivity in monkeys, 780
- Osborne, R. L.: Aberrant thyroid tumor of vertebrae with compression of spinal cord; recovery after operation and high voltage roentgen therapy, *277
 Early laminectomy for injury of spinal cord, 773
- Oxygen: See also Respiration
 studies on metabolism of brain suspensions; oxygen uptake, 911
- Pain: See also Sensation
 pathways for pain from stomach of dog, *739
- Palsy: See Paralysis
- Papilledema: See Neuritis, optic
- Papillitis: See Neuritis, optic
- Paraldehyde, visual hallucination during paraldehyde addiction, 913
- Paralysis: See also Extremities, paralysis; Eyes, paralysis; Poliomyelitis
 acute ascending; pathology and pathogenesis of Landry's paralysis, 134
 Bell's: See Paralysis, facial
 facial; bilateral agnesia associated with unilateral Bell's palsy, 926
 familial type in infants and its relationship to other hereditary familial disorders; clinico-pathologic study, *27
 General: See Dementia Paralytica
 Infantile: See Poliomyelitis
 Periodic: See Extremities, paralysis
 syndrome of involvement of posterior cord of brachial plexus, *860
- Paraphenylenediamine poisoning (ursol) with changes in central nervous system, *254
- Paresis: See Dementia Paralytica
- Parietal Lobe: See Brain
- Parotid Gland, disturbances in parotid secretion in unusual neurologic syndrome, *548
- Paskind, H. A.: Constitutional differences between deteriorated and nondeteriorated patients with epilepsy; capillaries of finger nail fold, *49
- Payne, J. T.: Atypical seizures elicited by electrical stimulation of cerebrum in cat, *244
- Pearson, G. H. J.: Reactions of people to war, 140
- Pentobarbital, Therapy: See Fever
- Persky, A.: Midbrain deafness; tumor of mid-brain producing sudden and complete deafness, *237
- Personality, acculturation processes and personality changes as indicated by Rorschach technic, 131
 electroencephalographic studies of psychopathic personalities, 916
 etiologic factors in adjustment of men in armed forces, 925
 incidence of neurosis in cases of bronchial asthma, 914
 investigation of personality in patients treated by prefrontal leukotomy, 292
 modified Rorschach technic for description of transitory postconvulsive personality states, 290
 psychopathology of ego system, 606
- Petry, H. K.: Symposium; complications of and contraindications to electric shock therapy, 787
- Phobias, fear of being buried alive, 606
- Phosphatides: See Lipoids
- Phospholipids: See Phosphorus and Phosphorus Compounds
- Phosphorus and Phosphorus Compounds, in vitro formation of phospholipid by brain and nerve with radioactive phosphorus as indicator, 284
 occurrence of sphingomyelin in tissues of cat, 285
- Physostigmine, studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of physostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
- Pipito, F. F.: Surgical history of trigeminal neuralgia, *574; correction, 791
- Pi-Suñer, J.: Experimental swelling of brain, *826
- Pituitary Body: See also Hypothalamus
 blood sugar in case of complete hypophysectomy, 136
 roentgenographic appearance of bones in Cushing's syndrome, 613
 structures of neurohypophysis with reference to nerve endings, 283
 suprasellar tumors related to pars intermedia of hypophysis, 287
 traumatic hemorrhage into pituitary gland, 603
 tuberculoma of hypophysis with insufficiency of anterior lobe, 137

- Platybasia: See Atlas and Axis; Occipital Bone
- Pneumococci, prognosis of pneumococcal meningitis treated with chemotherapy, 468
- Poisons and Poisoning: See under names of various substances, as Bromide and Bromine; etc.
- Polioencephalitis: See Encephalitis
- Polioencephalomyelitis: See Encephalomyelitis
- Poliomyelitis: See also Encephalomyelitis
acute anterior; analysis of 49 cases, 469
acute syphilitic anterior poliomyelopathy syndrome; report of case, *118
Kenny method of treatment of infantile paralysis, 310
- Pollock, L. J.: Effect of extremes of environmental change on man; president's address, *421
- Psychoneuroses of war, 924
- Polyradiculitis: See Nerves, roots
- Polyuria: See Diabetes Insipidus
- Pons Varolii, oculolaryngopharyngopalatine myoclonia in bulbopontile syndrome, 604
- Posture, experimental studies on headache: analysis of headache associated with changes in intracranial pressure, *323
- Potassium and muscular disorders, 294
in Urine: See Urine
relation of fibrillation to acetylcholine and potassium sensitivity in denervated skeletal muscle, 467
- Pregnancy: See Fetus; etc.
- Price, J. C.: Fascicular muscle twitchings in amyotrophic lateral sclerosis; their origin, *22
- Prisons and Prisoners, Medical Correctional Association, 771
- Prostigmine, effect on urinary excretion of potassium in normal subjects, 295
studies in diseases of muscle; progressive muscular atrophy; report of case with unusual features; effect of prostigmine and physostigmine on fasciculations; metabolism of ascorbic acid, *13
Therapy: See Myasthenia Gravis
- Psychiatry: See also Crime and Criminals; Hospitals; Insanity; Jurisprudence, Medical; Mental Diseases; Neuropsychiatry; Psychoanalysis; Psychology; Psychotherapy; War; etc.
Committee on War Psychiatry of American Psychiatric Association, 282
in war, 923
military, 915
military, symposium on, 909
problems in military aviation, 132
psychiatric study of man with convulsive disorder, 928
relations of psychoanalysis to, 140
value of formal psychiatric examinations in criminal court, 629
- Psychoanalysis: See also Psychotherapy
emotional settings of some attacks of urticaria, 914
fear of being buried alive, 606
incest and its effect on participants, 144
masochistic motives in criminal behavior, 630
microspia, 914
relations to psychiatry, 140
study of structural and instinctual conflicts in cases of hay fever, 607
Topeka Institute for, 282
- Psychology: See also Mental Tests; Personality; etc.
comparative; experimental neuroses and psychotherapy, *43
- Psychoneuroses: See Neuroses and Psychoneuroses
- Psychoses: See Insanity; Mental Diseases; Neuroses and Psychoneuroses; etc.
- Psychotherapy: See also Psychoanalysis and experimental neuroses, *43
ideation and trends encountered in psychotherapy of manic-depressive psychosis, 142
psychiatric study of man with convulsive disorder, 928
ward therapy, 611
- Puberty: See Adolescence
- Pulse, blood pressure and pulse changes in normal individuals under emotional stress; their relationship to emotional instability, 915
- Pupils, autonomic responses to electrical stimulation of forebrain and midbrain with reference to pupil, 466
catatonie, 918
- Putnam, T. J.: Amyotrophic lateral sclerosis and related conditions; clinical analysis, *151
Attempts at treatment of schizophrenia and other nonepileptic psychoses with diltantin, *414
- Pyramidal Tract, effect of precentral and postcentral cortical lesions on fiber components of pyramids in monkey, 285
pyramidal and extrapyramidal mechanisms in cortical control of movement, 782
pyramidal signs of upper extremity, 917
- Pyrexia: See Fever
- Rabies, pathogenesis and histopathology of hydrophobia in man, 605
- Races, application of Rorschach test to Samoan group, 608
- Radicle neuritis: See Nerves, root
- Radioactivity, in vitro formation of phospholipid by brain and nerve with radioactive phosphorus as indicator, 284
- Ranson, S. W.: Neurogenic hyperthermia and its treatment with soluble pentobarbital in monkey, *518
- Ray, B. S.: Experimental studies on headache; analysis of headache associated with changes in intracranial pressure, *323
- Recruits, etiologic factors in adjustment of men in armed forces, 925
military psychiatry, 915
reactions of people to war, 140
statistical control studies in neurology; Babinski sign, *272
- Reflex, Carotid: See Carotid Sinus
conditioned; origin and development of nervous disturbances experimentally produced, 129
conditioned reflex therapy of alcoholic addiction; follow-up report of 1,042 cases, 138
grasping; studies on corpus callosum; relationship of grasp reflex to section of corpus callosum, *820
pyramidal signs of upper extremity, 917
statistical control studies in neurology; Babinski sign, *272
- Respiration, effect of alkalosis and acidosis (producing changes in respiratory rate) on cortical electrical activity and blood flow, 286
- Restiform Body: See under Medulla Oblongata
- Reznikoff, L.: Comparison of metrazol convulsive therapy with electric shock in treatment of schizophrenia; evaluation of results obtained in treatment of 100 schizophrenic patients with electric shock, *587
- Richter, C. P.: Electrical skin resistance technique used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454
- Riggs, H. E.: Millary aneurysms; relation of anomalies of circle of Willis to formation of aneurysms, 615
- Riley, H. A.: Myasthenia gravis; familial occurrence, *904
- Risteen, W. A.: Studies on corpus callosum; relationship of grasp reflex to section of corpus callosum, *820
- Roche, P. Q.: Masochistic motives in criminal behavior, 630
- Roentgen Rays, Therapy: See under names of organs, regions and diseases, as Spine; etc.
- Roizin, L.: Myoclonus epilepsy; clinicopathologic report of case, 627
- Rorschach Test: See Mental Tests; Personality
- Rosenbaum, M.: Cerebral dysrhythmia in relation to eclampsia, *204

- Rosenbluth, A.: Control of clonic responses of cerebral cortex, 921
- Rosenzweig, S.: Sibling deaths in anamneses of schizophrenic patients, *71
- Ruch, T. C.: Primacy of area 13 of orbital surface of cerebral cortex in production of hyperactivity in monkeys, 780
- Rupp, C.: Miliary aneurysms; relation of anomalies of circle of Willis to formation of aneurysms, 615
- Russell, W. O.: Permanent damage to nervous system following attack of polyradiculoneuritis (Guillain-Barré syndrome); report of case, with necropsy, *895
- Sachs-Tay's Disease: See under Idiocy
- Saliva, disturbances in parotid secretion in unusual neurologic syndrome, 548
- Saltzman, M.: Midbrain deafness; tumor of midbrain producing sudden and complete deafness, *237
- Sarcoma: See also Tumors
circumscribed arachnoid sarcoma of cerebellum, 289
metastases; fibrosarcoma of arachnoidal origin with metastases, 288
of temporal lobe associated with abscess and invading subcutaneous extracranial tissues, 616
- Savitsky, N.: Statistical control studies in neurology; Babinski sign, *272
- Scarff, J. E.: Pseudojacksonian epilepsy in children, *223
- Scarlet Fever, scarlatinal encephalomyelitis, 619
- Scheinker, I. M.: Formation of demyelinated plaques associated with cerebral fat embolism in man, *754
Histogenesis of early lesions of multiple sclerosis; significance of vascular changes, *178
- Schizophrenia: See Dementia Praecox
- Schmale, H. T.: Clinical evaluation of mosaic test, 478
- Schools; School of Military Neuropsychiatry, 771
- Sciatica, diagnosis and surgical pathology of certain types of sciatic neuritis, 928
- Sclerosis: See also Arteriosclerosis
amyotrophic lateral, and related conditions; clinical analysis, *151
amyotrophic lateral, effect of vitamin E therapy on central nervous system in, 778
amyotrophic lateral, fascicular muscle twitchings in; their origin, *22
amyotrophic lateral; use of alpha tocopherol in treatment of neuromuscular disorders, 611
multiple; formation of demyelinated plaques associated with cerebral fat embolism in man, *754
multiple, histogenesis of early lesions of; significance of vascular changes, *178
- Selective Service: See Recruits
- Senile Plaque: See Sclerosis
- Senility: See Old Age
- Sensation: See also Pain; Taste; etc.
electrical skin resistance technic used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454
- Settlage, P. H.: Grouping behavior of normal persons and of persons with lesions of brain; further analysis, *489
- Sex, perversion; onism (transvestitism); report of case with additional outstanding psychopathic features, 635
perversion; masochistic motives in criminal behavior, 630
- Shenkin, H. A.: Primacy of area 13 of orbital surface of cerebral cortex in production of hyperactivity in monkeys, 780
- Sheps, J. G.: Frequency of convulsive disorders in feeble-minded; clinical and patho-anatomic considerations, 929
- Sherman, I. C.: Dr. H. Douglas Singer's concept of psychoses, *732
Eonism; report of case with additional outstanding psychopathic features, 635
- Singer, H. Douglas; his concept of psychoses, *732
- Skin: See also Sensation
calcification of cerebral cortex associated with meningotheliomatous meningioma; pathologic study, with comment on incomplete types of neurocutaneous syndrome, *507
electrical skin resistance technic used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454
studies of living nerves; growth adjustments of cutaneous terminal arborizations, 910
- Skull: See Cranium
- Sleep, disturbances; narcolepsy, 609
loss; effect of extremes of environmental change on man; president's address, *421
- Sloane, P.: Incest and its effect on participants, 144
Midbrain deafness; tumor of midbrain producing sudden and complete deafness, *237
- Smalldon, J. L.: Cachexia of mental origin; nature and management, 300
- Smell, study of structural and instinctual conflicts in cases of hay fever, 607
- Societies, American Board of Neurological Surgery, 282, 599
American Psychiatric Association, 909
Committee on War Psychiatry of American Psychiatric Association, 282
Medical Correctional Association, 771
- SOCIETY TRANSACTIONS:
American Association of Neuropathologists, 615
Boston Society of Psychiatry and Neurology, 308, 919
Chicago Neurological Society, 145, 475, 633, 924
Michigan Society of Neurology and Psychiatry, 478, 926
New York Neurological Society and New York Academy of Medicine, Section of Neurology and Psychiatry, 296, 773
Philadelphia Neurological Society, 479, 780
Philadelphia Psychiatric Society, 302, 629, 786
Philadelphia Psychiatric Society and Philadelphia Psychoanalytic Society, 140
- Sodium Amytal: See Mental Diseases
chloride; effect of hypertonic glucose solutions on inflow of normal saline solution into subarachnoid space of dog, 467
Diphenylhydantoinate: See Epilepsy
- Solandt, D. Y.: Effect of electrical stimulation on atrophy of denervated skeletal muscle, *802
- Spasm: See Convulsions; Epilepsy; etc.
- Spiegel, I. J.: Unusual complication of intraspinal use of iodized poppyseed oil, 926
- Sphingomyelin: See Phosphorus and Phosphorus Compounds
- Spiegel, E. A.: Cortical premotor and "post-motor" foci which influence gastrointestinal tract and their efferent pathways, 485
- Spiegel, L. A.: Disturbances in parotid secretion in unusual neurologic syndrome, *548
- Spinal Cord: See also Meninges; Nervous System; Pyramidal Tract; etc.
aberrant thyroid tumor of vertebrae with compression of spinal cord; recovery after operation and high voltage roentgen therapy, *277
cervical syringomyelia and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881
early laminectomy for injury of, 773
nervous system and regeneration of forelimb of adult Triturus; role of sympathetics, 911
origin, conduction and termination of impulses in dorsal spinocerebellar tracts (Flechsig's tract) of cats, 286
regenerative capacity of ventral roots after avulsion from spinal cord, *1
retrograde degeneration; effect of hemisections on homolateral axons of, *878

Spinal Cord—Continued

- spinal necrosis and softening of obscure origin; necrotic myelitis versus myelomaleia; review of literature and clinicopathologic case studies, *683
- topical organization and termination of fibers of posterior columns in *Macaca mulatta*, 510
- tumor of cauda equina with unusual onset and symptoms; report of case, 479
- unusual complication of intraspinal use of iodized poppyseed oil, 926
- Spinal Fluid: See Cerebrospinal Fluid
- Spinal Puncture: See also Cerebrospinal Fluid
 - experimental studies on headache; analysis of headache associated with changes in intracranial pressure, *323
 - treatment of post-lumbar-puncture headache with ergotamine tartrate, *556
- Spine: See also Atlas and Axis
 - aberrant thyroid tumor of vertebrae with compression of spinal cord; recovery after operation and high voltage roentgen therapy, *277
 - injuries of intervertebral disk in military service, 469
 - significance of vertebral fractures as complication of metrazol therapy, 612
 - spinal extradural cysts, 133
 - tumors; symptomatic herpes zoster, 135
 - unusual complication of intraspinal use of iodized poppyseed oil, 926
- Spinotriahamic Tract: See Medulla Oblongata
- Spirochetosis, licrohemorrhagic; optic neuritis following Weil's disease, 471
- Status and Staining, new staining method for demonstration of *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and *Histoplasma capsulatum* in histologic preparations, 621
- vascularization of cerebral neoplasms studied with fuchsin staining method of Eros, 626
- Status Epilepticus: See under Epilepsy
- Steinberg, D. L.: Etiologic factors in adjustment of men in armed forces, 925
- Stomach: See also Gastrointestinal Tract
 - pathways for pain from stomach of dog, *739
- Subarachnoid Space: See Meninges
- Subdural Spaces: See Meninges
- Subthalamus: See Hypothalamus
- Sugar in Blood: See Blood sugar
- Sulfide, neuropsychiatric sequelae of partial exsanguination, *594
- Suprarenal Preparations: See Adrenal Preparations
- Suprarenals: See Adrenals
- Surgery: See also Apparatus; Instruments; and under diseases, organs and regions
 - foreign body granulomas produced by surgical cotton, *581
 - surgical history of trigeminal neuralgia, *574; correction, 791
- Swank, R. L.: Amyotrophic lateral sclerosis and related conditions; clinical analysis, *151
- Fascicular muscle twitches in amyotrophic lateral sclerosis; their origin, *22
- Sympathectomy, electrical skin resistance technique used to map areas of skin affected by sympathectomy and by other, surgical or functional factors, *454
- preganglionic components of first thoracic nerve; their role in sympathetic innervation of upper extremity, 126
- Syphilis: See also Neurosyphilis; and under names of organs and regions
 - acute syphilitic anterior poliomyelopathic syndrome; report of case, *118
 - encephalopathy following intravenous administration of arsenical preparations, *863
- Syringomyelia, cervical, and syringomyelia-like states associated with Arnold-Chiari deformity and platybasia, *881

Tamaki, K.: Familial type of paralysis in infants and its relationship to other hereditary familial disorders; clinicopathologic study, *27

- Taste, bilateral ageusia associated with unilateral Bell's palsy, 926
- Tay-Sachs' Disease: See under Idiocy
- Taylor, J. H., Jr.: Symposium; complications of and contraindications to electric shock therapy, 789
- Testosterone: See Androgens
- Thalamus, afferent trigeminal pathways as determined by evoked potentials, 475
- Thale, T.: Effect of autonomic drugs on cerebrospinal fluid pressure in schizophrenic and other psychoses; effect of histamine, *449
- Thiamine: See also Vitamins, B
 - blood lactate-pyruvate relation and its use in experimental thiamine deficiency in pigeons, 127
 - study of deficiency in swine, 465
- Thrombosis: See also Embolism
 - bilateral, of posterior calcarine arteries with sparing of macular vision, 484
 - occlusion of anterior inferior cerebellar artery, *765
- Thymus, myasthenia gravis; treatment and relation to thymus, 476
- Thyroid, aberrant thyroid tumor of vertebrae with compression of spinal cord; recovery after operation and high voltage roentgen therapy, *277
- Tic Douloureux: See Neuralgia, trigeminal
- Tissue: See also Cells
 - development of late gastrula ectoderm in regenerating tissue of *Rana pipiens* larvae, 911
 - occurrence of sphingomyelin in tissues of cat, 285
 - study of nitrogenous constituents of tissue phosphatides, 285
- Tocopherol: See Vitamins, E
- Tones, effect of cortical destruction on responses to tones, 127
- Topeka Institute for Psychoanalysis, 282
- Tornay, A. S.: Spontaneous subarachnoid hemorrhage; analysis of 50 cases, 483
- Torula meningitis* (in association with Hodgkin's disease), 468
- new staining method for demonstration of *Debaryomyces neoformans* (*Torula histolytica*), *Blastomyces hominis*, *Coccidioides immitis* and *Histoplasma capsulatum* in histologic preparations, 621
- Tower, S. S.: Pyramidal and extrapyramidal mechanisms in cortical control of movement, 782
- Regenerative capacity of ventral roots after avulsion from spinal cord, *1
- Toxoplasmosis; toxoplasmic encephalitis; clinical experience, 315
- Tractotomy: See Medulla Oblongata
- Transference: See Psychoanalysis
- Transvestitism: See Sex, perversion
- Trauma: See Cranium, fractures; Head, injuries; etc.
- Tremors, apparatus to be used in recording tremors, *123
- Triorthoresyl Phosphate: See Cresyl Phosphates
- Tuber Cinereum: See Hypothalamus
- Tuberculoma of hypophysis with insufficiency of anterior lobe, 137
- Tuberculosis: See under names of various organs, regions and diseases
- Tuberulum Sellae: See Hypothalamus
- Tumors: See also Angioma; Cholesteatoma; Fibrosarcoma; Glioma; Lipoma; Meningioma; Microglioma; Sarcoma; Tuberculoma; and under names of organs and regions, as Brain; Cerebellum; Corpus Callosum; Cranium; Spinal Cord; Spine; etc.
 - intra cranial dermoid and epidermoid tumors, *56
 - metastases; symptomatic herpes zoster, 135
- Unconscious: See Psychoanalysis
- Uremia, chemical changes in blood and occurrence of uremia following head injury, 467
- Urine, effect of prostigmine on urinary excretion of potassium in normal subjects, 295

- Ursol: See Paraphenylenediamine
- Urticaria, emotional settings of some attacks of, 914
- Vaccinotherapy: See Neurosyphilis
- Van Wagenen, W. P.: Studies on corpus callosum; relationship of grasp reflex to section of corpus callosum, *820
- Vasomotor System: See Arteries; Capillaries
- Vascular, Pressure in: See Blood pressure
- Vertebrae: See Spine
- Vestibular Apparatus: See Ear
- Vision: See Medulla Oblongata
- Visual: See also Blindness
- Visual thrombosis of posterior calcarine sulcus with sparing of macular vision, 914
- Vitamins: See also Ascorbic Acid; Nicotinic Acid; Thiamine
- Vitamin E: See also Nicotinic Acid; Thiamine
- Vitamin E; cure of paralysis in rats with biotin concentrates and crystalline biotin, 285
- Vitamin E: See Thiamine
- Vitamin E: See Ascorbic Acid
- Vitamin E; effect of vitamin E therapy on central nervous system in amyotrophic lateral sclerosis, 778
- Vitamin E; some new applications of synthetic vitamin E therapy, 472
- Vitamin E; treatment of certain muscular atrophies with vitamin E with note on diagnosis and electromyograms, 138
- Vitamin E; effects of amounts of single vitamins of B group on rats deficient in other vitamins, 464
- Vitamin E; vitamin deficiencies and liver cirrhosis in alcoholism, 135
- Waggoner, R. W.: Frequency of convulsive disorders in feeble-minded; clinical and patho-anatomic considerations, 929
- Walsh, M. N.: Neuropsychiatric aspects of aviation medicine, 147
- War: See also Aviation and Aviators; Hospitals; Military Medicine; etc.
- War; and nervous disturbances, 916
- War; Committee on War Psychiatry of American Psychiatric Association, 232
- War; effect of extremes of environmental change on man; president's address, *421
- War; neuropsychiatry in wartime; president's address, 773
- War—Continued
- War; psychiatry in, 923
- War; psychoneuroses of, 924
- War; reactions of people to, 140
- Ward, J. W.: Atypical seizures elicited by electrical stimulation of cerebrum in cat, *244
- Watkins, A. L.: Kenny method of treatment of infantile paralysis, 310
- Weaver, H. M.: Pathways for pain from stomach of dog, *739
- Well's Disease: See Spirochætos, Icterohemorrhagic
- Weinberger, L. M.: Experiences with intramedullary tractotomy; immediate and late neurologic complications, *665
- Weinstein, E. A.: Functional representation in oculomotor and trochlear nuclei, *98
- Weston, K. R.: Cortical premotor and "post-motor" foci which influence gastrointestinal tract and their efferent pathways, 485
- Wheal: See Urticaria
- Whelan, F. G.: Electrical skin resistance technique used to map areas of skin affected by sympathectomy and by other surgical or functional factors, *454
- Whitehorn, J. C.: Schizophrenic language, *831
- Wills, Circle of: See Brain, blood supply
- Wilson's Disease: See Lenticular Nucleus, degeneration
- Winkelman, N. W.: Scarletinal encephalomyelitis, 619
- Wittman, M. P.: Etiologic factors in adjustment of men in armed forces, 925
- Wolff, H. G.: Experimental studies on headache; analysis of headache associated with changes in intracranial pressure, *323
- Wolff, H. G.: Studies in diseases of muscle; heredity of progressive muscular dystrophy; relationship between age at onset of symptoms and clinical course, *641
- Wolff, H. G.: Studies in diseases of muscle; progressive muscular dystrophy of atrophic distal type; report on family; report of autopsy, *655
- Wright, T. H., Jr.: Symposium; complications of and contraindications to electric shock therapy, 790
- Yaskia, J. C.: Spontaneous subarachnoid hemorrhage; analysis of 50 cases, 483
- Zeller, C. A.: Symposium; complications of and contraindications to electric shock therapy, 790
- Zipf, G. K.: Schizophrenic language, *831
- Zona: See Herpes zoster

